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Review of the Status of Knowledge on the Genetic Susceptibility of Indian Women for Polycystic Ovary Syndrome

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KEYWORDS Case-Control Studies. Distribution of Study Units. Future Perspectives. Genetic Association. Nature of Genes Studied. Single Nucleotide Polymorphisms

ABSTRACT A comprehensive and critical review of the genetic association studies of the polycystic ovary syndrome (PCOS) hitherto conducted in India was made and the information on allele frequencies for 104 variants from 52 genes with odds ratios and p-values, reflecting the patterns of association with PCOS presented. Only 23 different sample units were studied from 11 major cities of India and diabetes pathway genes/SNPs were studied more often than those from the other metabolic and reproductive pathways. Further, a relatively much wider spectrum of genetic variants were explored in the population of Hyderabad when compared to others. Overall, only 29 of the 104 variants studied were associated with PCOS ($p \leq 0.05$), eighteen of those being risk conferring with minor effects, hence not causative and in congruence with the global scenario. The researchers presented an assessment of the present status of genetic research on PCOS among Indian populations, identified the lacunae and future perspectives for research in India.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a complex endocrine and metabolic disorder affecting the reproductive aged women. The history of PCOS dates back to 1721 when Vallisneri described a married and infertile woman with shiny and white surfaced ovaries with size similar to the pigeon eggs (Insler and Lunesfeld 1990). However, this disorder was first described in 1935 by Stein and Leventhal in the women with menstrual disturbances, hirsutism, and enlarged ovaries containing many small follicles (Stein and Leventhal 1935) and was thus initially come to be known as Stein-Leventhal syndrome. Subsequent research demonstrated that it is no longer a disorder limited to the ovaries, but involves various other organ systems in its complex pathophysiology. The PCOS is characterized by hyperandrogenism, chronic anovulation and cystic ovarian morphology and is the leading cause of infertility. It is associated with obesity and increased risk for type 2 diabetes (T2DM), cardiovascular diseases (CVDs), endometrial cancers and psychological problems (Azziz et al. 2016). Because of its complex etiology and pathophysiology, PCOS is considered as a complex disorder whose manifestation is the consequence of a number of genetic and environmental factors and their interactions. However, its etiology remains still uncertain due to a number of reasons. In general, the genetic studies of PCOS were limited when compared other complex disorders like T2DM, coronary heart diseases and cancers. A comprehensive review of the global status of molecular genetic studies on the PCOS was undertaken, probably for the first time, by Dasgupta and Reddy (2008), which highlighted a number of important aspects of this research:

1. The highly inconsistent nature of the results of genetic association studies in that a relatively greater proportion of the studies showed lack of association than those that did with reference to any particular gene/SNP studied.
2. A relatively small size of the samples were used for most of the studies, which lacked statistical power and because of the variable diagnostic criteria for PCOS used by different investigators yielded wide range of prevalence rates across ethnic groups/ geographic populations.

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3. The inconsistency in the results of association was attributed to be due to lack of statistical power and variable diagnostic criteria for PCOS used in different studies that resulted in the phenotypic heterogeneity of the PCOS cases.
4. Virtually no genetic association study of PCOS was conducted among the Indian populations and that most Indian PCOS studies were focused only on the clinical dimensions.

Subsequently, there have been many genetic association studies on PCOS globally and as well as in India. To date, more than 100 candidate genes have been studied through candidate gene approach and 16 genes/ loci were identified recently through GWAS. During the past 10 years, ~104 variants belonging to 52 genes have been screened among the Indian women in the pursuit of understanding the nature of their susceptibility for PCOS.

Objective

The primary objective of the present study was to critically review the genetic association studies so far conducted among the Indian populations and to gauge the present status of understanding of the genetic susceptible patterns of the Indian women with PCOS. However, for the benefit of readership, the researchers have also provided a brief overview of the different diagnostic criteria used in recruiting PCOS cases, pathophysiological mechanisms involved in the manifestation of this syndrome and the present global status of genetic research on PCOS.

Diagnostic Criteria

The details of different diagnostic criteria used in identifying PCOS are furnished in Table 1. The PCOS was first defined by NICHD (National Institute of Child Health and Human Development) conference in the year 1990, which was revised by Rotterdam Consensus Workshop in 2003 (Rotterdam 2004). Subsequently, the Androgen Excess Society in 2006 has combined the above two criteria and came up with the third criteria according to which the presence of clinical or biochemical hyperandrogenism and either oligo-anovulation or polycystic ovarian morphology is required for diagnosis of PCOS. This has resulted in the inherent phenotypic heterogeneity of the PCOS samples drawn, which had become a challenge for human geneticists delaying the progress in the genetic dissection of the syndrome. Therefore, the NIH in 2012 addressed the benefits and drawbacks of the existing diagnostic criteria and came up with a broader version of ESHRE/ASRM 2003 criteria along with a detailed description of the PCOS phenotypes (National Institutes of Health 2012) that could be specific targets of genetic investigations.

Pathophysiology

The pathophysiological mechanisms of PCOS are depicted in the schematic diagram (Fig. 1). The most prominent features of PCOS- hyperandrogenism, polycystic ovaries and metabolic abnormalities- appear to have interconnecting roles in the manifestation of PCOS. Most women with PCOS have elevated levels of luteinizing hormone (LH) and reduced levels of follicle stimulating hormone (FSH) along with elevated levels of androgens and insulin, which can manifest as oligomennorhea or amenorrhea. Excessive production of androgens by the ovaries and adrenals result in a number of additional features like tiny cysts on the ovaries, hirsutism and acne. Insulin resistance, which occurs independently of obesity in PCOS, may affect ovulation and fertility by interfering with hepatic production of sex hormone binding globulin (SHBG). Reduced levels of SHBG levels lead to an increase in free testosterone levels. The combination of anovulation and hyperinsulinemia can promote endometrial cell proliferation, increasing the risk of endometrial carcinomas and other abnormalities. In addition to glucose and insulin abnormalities, CVD risk factors (like hypertension, dyslipidemia, and impaired blood vessel function) often accompany PCOS. For further details on the pathophysiological mechanisms of this syndrome one may refer to Dasgupta and Reddy (2008).

Etiology

Although the etiology of PCOS remains uncertain, it is considered as a multi-factorial disorder with various genetic, metabolic, endocrine

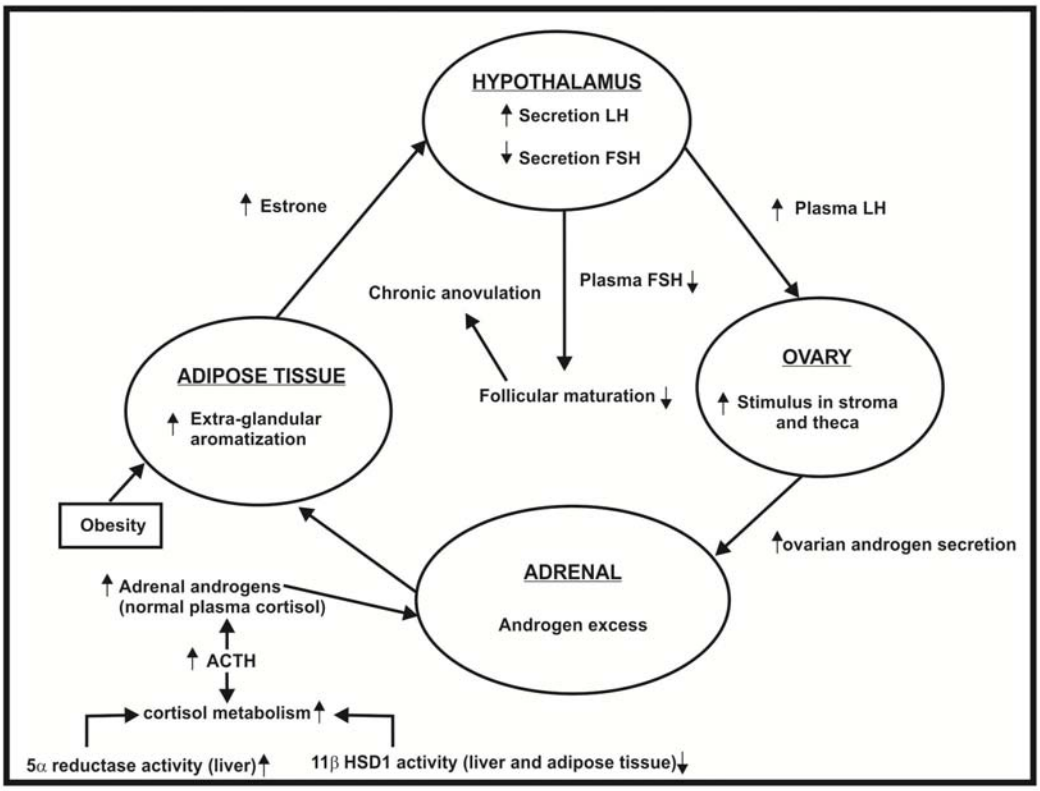

Fig. 1. The Schematic representation of different pathophysiological mechanisms involved in the manifestation of PCOS. (Adapted from Dasgupta and Reddy 2008).

and environmental abnormalities (Franks et al. 2006). The familial and twin studies indicate a strong genetic and heritable component in PCOS (Mykhalchenko et al. 2017). However, it is believed that utero-fetal programming may have a significant role in the manifestation of PCOS in the adult life. Further, despite a woman being genetically predisposed to the disease, it is only through the interactions of environmental and genetic factors that might ultimately lead to PCOS phenotype (Allahbadia and Merchant 2008). The highly variable phenotype of PCOS suggests that apart from genes, environmental influences such as obesity, peripubertal stress and/or hormonal exposures may contribute to the manifestation of the disease (Kahsar-Miller and Azziz 1998).

Genetic Association Studies

Two approaches that are employed in identifying the genetic loci for PCOS are linkage and association studies (Unluturk et al. 2007). The case-control design used in genetic association studies has been the powerful tool for studying the genetic susceptibility profile of the complex genetic diseases (Risch and Merikangas 1996). In the linkage studies, the proband and their families are investigated to determine if the particular genomic landmarks are distributed independently or in linkage with the phenotype. However, linkage studies are robust in identifying single gene causing Mendelian disorders but are poorly suited to study complex traits like PCOS.

Findings of Candidate Gene Approach: An Overview of the Global Scenario

The genetic susceptibility of PCOS has been widely examined by candidate gene association studies involving more than 100 genes and focusing around the genes responsible for steroidogenesis (CYP1A1, CYP11A, CYP17A1,

Table 1: Diagnostic criteria for polycystic ovary syndrome

	NICHD/1990	*ESHRE/ASRM Rotterdam/2003*	*AES/2006*	*NIH 2012(extension of ESHRE/ASRM 2003)*
Diagnostic Criteria	Requires the simultaneous presence of 1. Clinical and/or biochemical hyperandrogenism 2. Menstrual dysfunction	Requires the presence of at least two criteria: 1.clinical and/or biochemical hyperandrogenism, 2. Ovulatory dysfunction 3. PCOM	Requires the presence of hyperandrogenism, Clinical or biochemical, and either: 1. Oligo-anovulation or 2. PCOM	Requires the presence of any two of the three 1.Hyperandrogenism 2.Ovulatory dysfunction 3.PCOM with specific phenotypes included A- hyperandrogenism + ovulatory dysfunction + PCOM B- hyperandrogenism + ovulatory dysfunction C- hyperandrogenism + PCOM D- ovulatory dysfunction + PCOM
Exclusion Criteria	Congenital adrenal hyperplasia, androgen secreting tumours, Cushing syndrome, hyperprolactinaemia	Congenital adrenal hyperplasia, androgen secreting tumours and Cushing's syndrome	Congenital adrenal hyperplasia, androgen secreting neoplasms, androgenic/anabolic drug use or abuse, Cushing's syndrome, syndromes of severe insulin resistance, thyroid dysfunction and hyperprolactinaemia	Congenital adrenal hyperplasia, androgen secreting tumours and Cushing's syndrome
Clinical Traits	Hirsutism, alopecia and acne	Hirsutism, acne and androgenic alopecia	Hirsutism	Hirsutism, acne and androgenic alopecia
Biochemical Traits	1. Total testosterone 2. Free testosterone 3. Androstenedione 4. DHEA	1. Free androgen index or free testosterone 2. Total testosterone 3. DHEA	1. Free androgen index or free testosterone 2. Total testosterone 3. DHEA 4. Androstenedione	1. Free androgen index or free testosterone 2. Total testosterone 3. DHEA
PCOM	Not included	At least one ovary showing either: 1. Twelve or more follicles (2-9 mm in diameter) or 2. Ovarian volume - 10 ml	At least one ovary showing either 1. Twelve or more follicles (2-9 mm in diameter) or 2. Ovarian volume - 10 ml	At least one ovary showing either: 1. Twelve or more follicles (2-9 mm in diameter) or 2. Ovarian volume - 10 ml

NICHD - National Institute for Child Development and Human Diseases, AES - Androgen Excess Society, PCOM - polycystic ovary morphology, DHEA - dehydroepiandrosterone, adapted from Dasgupta and Reddy, (2008) and modified.

CYP19, HSD17B6, AR, SHBG, SRD5A1 and SRD5A2), folliculogenesis (FSHR, LHCGR and AMHR2), insulin signaling (IRS1, IRS2, INSR, PPARγ and CAPN10), energy homeostasis (ADIPOQ and FTO) and chronic inflammation (IL-1α, IL-1β, IL6, IL18, PAI1, FBN3, TNF and MEP1A). However, till date, none of the candidate genes identified was found to be causative to the disease. The PCOS candidate genetic studies have been hampered by various limitations, which include the complex genetic architecture, incomplete characterization of phenotype in family members, small sample size and phenotype heterogeneity. However, presently, a few attempts are being made to overcome some of these limitations by considering larger number of pheno-

type specific patients and controls and by further confirming the association by considering cohorts of discovery and independent replication. Furthermore, candidate gene findings are being confirmed by using family based approaches like TDT (transmission disequilibrium test) (Mykhalchenko et al. 2017).

Genome Wide Association Studies

For the complex genetic disorders like PCOS, GWAS provides an important tool as the analyses do not rely on a molecular mechanism hypothesized a priori (Mykhalchenko et al. 2017). To date, five GWAS studies have been performed (Table 2) in the populations of Han Chinese (Chen et al. 2011; Shi et al. 2012), Koreans (Lee et al. 2015) and European (Day et al. 2015; Hayes et al. 2015) and identified several novel susceptible loci for PCOS (Table 2).The GWAS in Han Chinese identified 11 risk loci (3 loci from first GWAS and 8 loci from second GWAS in addition to confirming the 3 previously identified loci). Further, a TDT performed to study the association between PCOS trios and all the SNPs in the susceptibility loci from first and second GWAS, confirmed the association of rs13429458 (THADA) from first GWAS (Zhao et al. 2012) and rs2349415 (FSHR) and rs3802457 (c9orf3) from second GWAS (Zhao et al. 2015) with PCOS. Following the Chinese GWAS studies, several replicate studies were performed in other ethnic populations. A two stage GWAS in Korean women identified only moderately associated loci in the first study, but in the second stage study, a promising risk locus on chromosome 8q24.2 in KHDRBS3 gene was identified (Lee et al. 2015). The European GWAS (Day et al. 2015; Hayes et al. 2015) identified two novel loci- 8p32.1 (GATA4/NEIL2) and 11p14.1 (FSHB/ARL14EP) and one locus 9q22.32 (c9orf3/FANCC), which was already reported in the first study of Chinese (Shi et al. 2012). The second GWAS identified six signals (Day et al. 2015) of which three were previously reported and three novel- rs1351592 located on 2q34 (ERBB4/HER4); rs13164856 located on 5q31.1 (RAD50) and rs1275468 located on 12q21.2 (KRR1). The foregoing observations suggest the possibility of identifying unique patterns of genetic susceptibility to PCOS among different ethnic and/or geographic populations. For detailed account on the global status of genetic research on PCOS, one may refer to the recent review by Mykhalchenko et al. (2017).

Research on the Polycystic Ovary Syndrome in the Indian Context

Due to urbanization and changing lifestyles, there has been an increasing prevalence of PCOS in the recent decades in India and other developing countries. The recent reports from the Indian infertility clinics suggest that ~ 60 percent of those coming to these clinics suffer from PCOS and the overall prevalence is estimated at ~ 20 percent among the Indian women in reproductive age (Malathy 2016). It's such an emerging health problem of national concern that the Indian Council for Medical Research (ICMR) has recently inaugurated a special clinic at National Institute for Research in Reproductive Health (NIRRH), Parel, Mumbai, with an idea of evolving model PCOS clinics that can be replicated in public hospitals across the country. The South Asian women were reported to have more severe reproductive and metabolic complications than the other ethnic groups. For instance, South Asians with PCOS have higher degree of hirsutism, infertility and acne and seek medical care at an earlier age for reproductive abnormalities. Likewise they also exhibit a higher prevalence of insulin resistance and metabolic syndrome than the other ethnic groups with similar BMI (Mehta et al. 2013). Before focusing on the outcome of genetic association studies of PCOS, a brief overview of the outcome of clinical and other epidemiological studies in India are provided for the sake of an overall understanding of the research on this syndrome.

Clinical Studies on PCOS from India

There have been a large number of clinical studies on the Indian populations as compared to the genetic association studies. These studies have examined various aspects in relation to PCOS and the findings are briefly outlined in the Supplementary Table 1, which suggest higher incidence of insulin resistance, T2DM, dyslipidemia, oxidative stress, carotid intima medial wall thickness (CIMT) in PCOS as compared to the normal women. Also, the dysregulation in plasma amino acid, carbohydrate/lipid and purine and protein metabolism was found among them. The association of increased psychological dis-

Table 2: Genes/SNPs identified through genome wide association studies of PCOS

Population/ Sample size	*Locus*	*Nearby gene/ Gene*	*SNP*	*Odds ratio*	*P value*	*Function/ Associated disease*	*Reference*
Han Chinese Discovery phase-744 PCOS , 895 controls Replication phase (2 independent cohorts)	2p21	THADA	rs13429458	1.49	1.73×10^{-23}	Diabetes genes	(Chen et al. 2011)
			rs12468394	1.38	1.59×10^{-20}		
			rs12478601	1.39	3.48×10^{-23}		
1-2840 PCOS, 5012 controls (Northern Han Chinese); 2-498 PCOS, 780 controls (Southern and Central Han Chinese)	2p16.3	LHCGR	rs13405728	1.41	7.55×10^{-21}	Folliculogenesis and ovulation	
	9q33.3	DENND1A	rs2479106	1.34	8.12×10^{-19}	Regulates Rab GTPases and involves in exocytosis of gonadotropins	
			rs10818854	1.51	9.40×10^{-18}		
			rs10986105	1.47	6.90×10^{-15}		
Han Chinese Discovery phase-2254 PCOS , 3001 controls Replication phase (2 independent cohorts)	2p16.3	FSHR	rs2268361	1.14	9.89×10^{-13}	Gonadotropin action	(Shi et al. 2012)
			rs2349415	1.19	2.35×10^{-12}		
1-1908 PCOS,1913 controls; 2-6318 PCOS, 5665 controls	9q22.32	C9orf3	rs4385527	1.19	5.87×10^{-9}	Aminopeptidase activity	
			rs3802457	1.29	5.28×10^{-14}		
	11q22.1	YAP1	rs1894116	1.27	1.08×10^{-22}	Controls organ size and cell proliferation	
	12q13.2	RAB5B/ SUOX	rs705702	1.27	8.64×10^{-26}	Type 1 diabetes	
	12q14.3	HMGA2	rs2272046	1.42	1.95×10^{-21}	Controls organ size and cell proliferation	
	16q12.1	TOX3	rs4784165	1.15	3.64×10^{-11}	Chromatin remodelling	
	19p13.3	INSR	rs2059807	1.14	1.09×10^{-8}	Diabetic genes	
	20q13.2	SUMO1P1	rs6022786	1.13	1.83×10^{-9}	Controls organ size and cell proliferation	
	2p21*	THADA	rs13429458*	1.49	4.17×10^{-13}		
	2p16.3*	LHCGR	rs13405728*	1.35	3.77×10^{-9}		
	9q33.3*	DENND1A	rs2479106*	1.35	5.14×10^{-10}		

Table 2: Contd...

Population/ Sample size	*Locus*	*Nearby gene/ Gene*	*SNP*	*Odds ratio*	*P value*	*Function/ Associated disease*	*Reference*
Korean Discovery phase-976 PCOS , 946 Controls; Replication phase 249 PCOS, 778 controls	8q24.2	KHDRBS3	rs10505648	1.92	5.46×10^{-8}	Telomerase activity	(Lee et al. 2015)
Caucasians Discovery phase-984 PCOS , 2964 Controls;	8p32.1	GATA4/ NEIL2	rs804279	1.35	8.0×10^{-10}	Folliculogenesis/DNA repair	(Hayes et al. 2015)
First replication phase- 1799 PCOS , 1231 controls; Second replication phase- 217 PCOS,1335 controls	11p14.1	FSHB/ ARL14EP	rs11031006	1.12	1.9×10^{-8}	Folliculogenesis	
	9q22.32*	c9orf3/ FANCC	rs10993397	1.39	4.6×10^{-13}		
Caucasians Discovery phase-5184 PCOS , 82,759 Controls; Replication phase- 2000 PCOS , ~1,00,000 controls	2q34	ERBB4/ HER4	rs1351592	1.18	1.2×10^{-12}	Epidermal growth factor	(Day et al. 2015)
	5q31.1	RAD50	rs13164856	1.13	3.5×10^{-9}	DNA double strand break repair	
	12q21.2	KRR1	rs1275468	1.13	1.9×10^{-8}	Unknown	
	11p14.1*	FSHB	rs11031006*	1.16	1.3×10^{-9}	Folliculogenesis	
	2p21*	THADA	rs7563201	1.13	3.3×10^{-10}	Diabetes genes	
	11q22.1*	YAP1	rs11225154	1.22	7.6×10^{-11}	Cell proliferation and survival, tissue repair and tumorigenesis	

*- Loci/ SNPs identified in the earlier GWAS studies also.

tress with endocrine disturbances, hypothyroidism, Grave's disease, sleep disorders and increased metabolic risk was observed in PCOS women. The reviews of clinical aspects of PCOS among the Indians were attempted by Allahbadia and Merchant (2008) and Keziya et al. (2017), whereas the review of multi-omic studies dissecting pathophysiology of PCOS was done by Sagvekar et al. (2018). Further, studies concerning the role of anti mullerian hormone (AMH) in the diagnosis of PCOS (Singh and Singh 2015), relationship between bone mineral density and hormonal changes in PCOS (Krishnan and Muthusami 2017) and pathophysiological mechanisms linking periodontal disease and PCOS (Tanguturi and Nagarakanti 2018) were also undertaken.

Studies on Adolescent Girls

A few studies on the prevalence of PCOS among the Indian adolescents and young girls (Bhattacharya and Jha 2011; Nidhi et al. 2011; Gill et al. 2012; Joshi et al. 2014) were undertaken and the prevalence was estimated to be 9.13 percent among them (Nidhi et al. 2011). Besides the prevalence studies, other problems like menstrual irregularity (Nair et al. 2012), euthyroid chronic lymphocytic thyroiditis (Ganie et al. 2010), sympathovagal imbalance and neurophysiologic cognitive assessment using evoked potentials (Velusami and Sivasubramanian 2018) were investigated in adolescents.

Other Studies

An epidemiological survey on predisposing factors of PCOS in the urban and rural south Indian populations showed urban women are prone to get PCOS more frequently than rural women and that the positive family history to have strong association with PCOS (Vidya et al. 2017). Considering autosomal dominant nature of PCOS in females, it has been suggested that same can be expressed in males as premature androgenic alopecia (AGA) (Dusková et al. 2004). With reference to similarity of hormonal profiles of men with premature AGA and PCOS in women, hypothesis of existence of a male PCOS equivalent in men with premature AGA was put forward and investigated in India (Narad et al. 2013; Sanke et al. 2016). Further, a meta-analysis on Ischemia modified albumin (IMA) levels suggests that it could be considered as a marker for increased oxidative stress in PCOS (Seshadri et al. 2018). The effects of certain drugs like Metformin, ethinyl estradiol, desogestrel, letrozole, inositols and a few others have also been examined in PCOS women for the management of the disease. Further**,** a Knowledge base for genes, diseases, ontology terms and biochemical pathways associated with Polycystic Ovary Syndrome (PCOSKB) was developed (Joseph et al. 2016). Another online resource, Polycystic Ovary Syndrome Data Base (PCOSDB) was developed which contains manually curated information from 234 published sources (Jesintha et al. 2016). The Indian Fertility Society (IFS) founded in 2005 published the first practice guideline on the management of PCOS in the country. They have recommended one clinical and one biochemical index as risk factors for developing PCOS (Malik et al. 2016).

Indian Genetic Studies

Procedures for Data Compilation

The literature search for PCOS genetic studies in India was done in PubMed database and Google website (www.google.com) and a number of pertinent International and Indian journals using keywords such as 'PCOS'/ 'polycystic ovary syndrome', 'India', 'genetic research', 'association studies' and 'candidate genes' in various combinations. Further, for papers with no provision for free online access, the respective authors were contacted with request for PDF version of the articles. The last search was performed on February 28th 2019.

Observations on the Indian Genetic Studies

The genetic studies of PCOS in India are limited and restricted to samples from a few major cities (Fig. 2). While the control samples were recruited from the general population of the respective areas, the sources of case sample collection for different sampling units within each of these cities along with the sample sizes are furnished in Table 3. Whereas six independent samples were investigated from Hyderabad metropolitan area itself, five samples from Chennai, two each from Delhi, Kolkata and Coimbatore and one each from Mumbai, Amritsar, Rohtak, Mangalore, Varanasi and Kashmir were studied. However, broadly speaking, the genes/SNPs

Fig. 2. The geographic distribution of PCOS studies in India. The alpha numeric characters represent independent study units of the respective locations. $ Mixed Sample: CV-Chennai and Varanasi CMK-Coimbatore and Kerala

considered in different samples from the same city and/or among different city samples in India are largely non-overlapping. The results on the nature of association of different genes/SNPs with PCOS are presented in Table 4, and discussed according to different pathways. The initial genetic studies on PCOS have focused primarily on hyperandrogenism and ovarian dysfunction related candidate genes (M1-Anurupa et al. 2004; H5-Babu et al. 2004; H1- Dasgupta et al. 2010, 2012b, 2012c; Rajender et al. 2013). However, there has been a gradual shift towards studying the genes implicated in metabolic aspects of the disease due to its association with insulin resistance, hyperinsulinemia and obesity, which increase the risk for developing T2DM, CVDs and endometrial cancers. Till date, about 104 variants belonging to 52

Table 3: Study locations with respective sources of case sample collection for the PCOS studies in India

Study population	*Sampling unit*	*Source of case samples*	*Sample size* Case/control*
Kashmir,Jammu and Kashmir	KS1	Department of Endocrinology, Sher-i-Kashmir, Institute of Medical Sciences (SKIMS)	220/220
Amritsar,Punjab	A1	Hartej Hospital	250/250
Rohtak,Haryana	R1	Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences (PGIMS)	200/200
New Delhi	ND1	Department of Gynecology and Obstetrics and HAH Centenary Hospital	95/45
	ND2	Vardhman Mahavir Medical College and Safdarjang Hospital	50/50
Varnasi,Uttar pradesh	V1	Information not given	92/97
Kolkata, West Bengal	K1	Burdwan Medical College and National Medical College	75/73
	K2	ILS hospital	125/82
MumbaiMaharashtra	M1	National Institute for Research in Reproductive Health (NIRRH), Seth GS Medical College and KEM Hospital	516/424
Hyderabad, Telangana	H1	Osmania General Hospital, Anu Test Tube Baby Centre	250/299
	H2	Modern Government Maternity Hospital	281/299
	H3	Infertility Institute and Research Centre (IIRC)	126/130
	H4	Different obstetrics and Gynecology Centres	204/204
	H5	IIRC	180/72
	H6	Owaisi Hospital and Research Centre	219/272
Mangalore,Karnataka	MN1	Kasturba Medical College, Mangalore	100/100
Chennai,Tamilnadu	C1	ARC Research and Fertility Centre	30/30
	C2	Information not given	169/169
	C3	SMART clinic, Department of Reproductive Medicine	97/101
	C4	Information not given	43/43
	CV[$]	Maaruthi Medical Centre and Hospitals (Erode)	261/256
Coimbatore,Tamilnadu	CMK[$]	Health Centre and Private Fertility Clinic	282/200
	CM1	Tertiary Care Hospital	75/75

*The maximum sample size; sample size may vary in different publications based on the same unit of study; study wise sample size can be found from Table 4. $-Mixed sample-(CV-Chennai and Varanasi; CMK-Coimbatore and Kerala)

genes of various pathways have been studied among the Indians and the relative proportions of genes studied from different pathways are presented in Table 5. Very few studies have considered the genes belonging to both reproductive and metabolic pathways (H1-Dasgupta and Reddy 2013; M1- Dadachanji et al. 2015, 2018; Shaikh et al. 2016; H3-Siddamalla et al. 2018a, 2018b; Reddy TV et al. 2018). Further, based on 15 most significant SNPs of the nine T2DM genes screened in a sample of 250 PCOS women and similar number of controls from Hyderabad-H1, Reddy BM et al. (2016) addressed the issue of lack of association of type 2 diabetes related genes with PCOS earlier observed in other ethnic groups and found concurrent results in the population of Hyderabad, which prompted them to surmise if this phenomenon of lack of association is not universal. Based on the above results, it was also hypothesized that (1) there could be other T2DM genes (other than those considered in their study) that play a more significant role in PCOS and (2) it may not be diabetes genes per se but their interaction with more crucial reproductive pathway genes that might play a role in the manifestation of PCOS. In order to test these hypotheses, the researchers are currently exploring a large set of 92 SNPs genotyped in the same cohort and representing both metabolic and reproductive pathway genes to examine if any of the type 2 diabetes genes or their interactions with reproductive pathway genes were significantly associated with PCOS, which may help in the process of establishing probable universality of the pattern of lack of association of T2DM genes with PCOS. A couple of studies have also focused on epigenetic mechanisms by X-Chromosome inactivation pattern by considering CAG repeats but association was not observed (Dasgupta et al. 2010; Rajender et al. 2013), even in the subsequent meta-analysis (Rajender et al. 2013).

Table 4: Candidate genes for PCOS studied in India along with their SNPs, allele frequencies and the results of logistic regression analysis

S. No.	*Gene*	*Population sample size (Case/Control) Reference*	*Studied variants*	*Major/ Minor allele*	*Allele frequency (%)* *Case*	*Control*	*Odds ratio (CI)*	*P value*	*Function*
Reproductive Pathway Genes									
1	CYP1A1 (Cytochrome P450 family 1 sub family A member1)	Varanasi (V1) 100/100 Jain et al. 2015	rs6235	T C	0.71 0.28	0.78 0.22	1.40 (0.89-2.21)	0.14	Xenobiotic-metabolizing enzyme of the placenta
		Hyderabad (H5) 180/72 Babu et al. 2004	rs6235	T C	*0.88* *0.11*	*0.83* *0.16*	*0.64(0.28-1.47)*	*0.3*	
2	CYP11A1 (Cytochrome P450 family 11 sub family A member1)	Hyderabad (H2) 267/275 Reddy KR et al. 2014	$(tttta)_n$ polymorphism* <8 repeat 8 repeat >8 repeat	— — —	0.21 0.15 0.64	0.38 0.24 0.38	0.42(0.29-0.62) 0.55(0.35-0.85) 2.93(2.06-4.15)	<0.0001 0.008 <0.001	Conversion of cholesterol into progesterone
		Mumbai (M1) 30/25 Anurupa et al. 2004	Exons 3,4 & 9	—	—	—	—	No variants	
3	CYP17A1 (Cytochrome P450 family 17 sub family A member1)	Amritsar (A1) 250/250 Kaur et al. 2018 Kolkata (K1) 75/73 Banerjee et al. 2016	rs743572 C/T polymorphism in -34 promoter region	T C C T	0.66 0.34 0.51 0.48	0.77 0.23 0.52 0.47	*1.72(0.92-3.21)* (0.945)[$]	*0.08* **0.0005** 0.8	Involves in steroidogenic pathway
4	CYP19A1 (Cytochrome P450 family 19 sub family A member1)	Amritsar (A1) 250/250 Kaur et al. 2018	rs700519 rs2414096	C T G A	0.8 0.2 0.92 0.08	0.82 0.18 0.94 0.06	*1.13(0.56-2.31)* *1.34(0.32-5.43)*	*0.71* **0.63** *0.68* **0.61**	Involves in estrogen biosynthesis
		Hyderabad (H2) 249/257 Ranjith et al. 2015	rs700519 rs2414096 rs60271534	C T G A S L	0.54 0.46 0.54 0.46 0.7 0.3	0.64 0.36 0.5 0.5 0.7 0.3	1.51(0.85-2.66) 0.85(0.48-1.48) 1(0.54-1.83)	0.19 0.67 1	
5	FSHR (Follicle Stimulating Hormone Receptor)	Chennai (C3) 97/101 Kambalachenu et al. 2014	rs1394205 rs6165 rs6166	G A G A A G	0.65 0.35 0.54 0.46 0.59 0.41	0.63 0.37 0.59 0.41 0.56 0.44	*0.91(0.51-1.63)* *1.22(0.70-2.14)* *0.88(0.50-1.54)*	*0.76* *0.47* *0.66*	Gonad development

Table 4: Contd...

S. No.	*Gene*	*Population sample size (Case/Control) Reference*	*Studied variants*	*Major/ Minor allele*	*Allele frequency (%)*		*Odds ratio (CI)*	*P value*	*Function*
					Case	*Control*			
		Hyderabad (H4) 204/204 Thathapudi et al. 2016	rs6166*	A G	0.61 0.39	0.44 0.56	*0.50(0.28-0.88)*	*0.01*	
6	FST (Follistatin)	Hyderabad (H1) 250/299 Dasgupta et al. 2012c	All exons	—	—	—	—	No association	Activin antagonist
7	HSD11B1 (Hydroxysteroid 11 Beta-Dehydrogenase 1)	Mangalore (MN1) 100/100 Devang et al. 2018	rs12086634*	T G	0.8 0.2	0.89 0.11	1.95(1.11-3.44)	0.01	Reduces cortisone to active hormone cortisol.
			rs846910	G A	0.9 0.1	0.84 0.16	0.57(0.31-1.05)	0.07	
8	LHCGR (Leutinizing hormone/ choriogonadotropin receptor)	Hyderabad (H4) 204/204 Thathapudi et al. 2015a	rs2293275*	A G	0.4 0.6	0.51 0.49	1.53(1.16-2.01)	0.002	Development of Leydig cells
9	LH β (Lutenizing hormone beta)	Hyderabad (H1) 250/299 Dasgupta et al. 2012b	rs1800447	T C	0.96 0.03	0.95 0.04	0.93(0.50-1.73)	0.83	Responsible for LH specificity
			rs34349826	T C	0.96 0.03	0.95 0.04	0.93(0.50-1.73)	0.83	
			rs6521	G C	0.5 0.49	0.51 0.48	1.04(0.82-1.30)	0.7	
			rs1056914	C A	0.44 0.55	0.49 0.5	1.21(0.95-1.54)	0.11	
			rs2387588	C T	0.52 0.47	0.51 0.48	1.02(0.80-1.30)$	0.82	
			rs4287687	CAG C-G	0.6 0.39	0.65 0.34	1.23(0.95-1.57)	0.1	
			rs1056917*	T C	0.51 0.48	0.58 0.41	1.34(1.05-1.72)	0.01	
10	SHBG (Sex Hormone Binding Globulin)	Rohtak (R1) 200/200 Bhatnager et al. 2019	rs6259	G A	0.93 0.07	0.95 0.05	*1.40(0.32-6.10)*	*0.65*	Transporter protein and regulates the bioavailability of androgens.

Table 4: Contd...

S. No.	*Gene*	*Population sample size (Case/Control) Reference*	*Studied variants*	*Major/ Minor allele*	*Allele frequency (%)* *Case*	*Control*	*Odds ratio (CI)*	*P value*	*Function*
Type 2 Diabetes Genes									
11	CAPN10 (Calcium activated cysteine protease)	Hyderabad (H1) 250/299 Dasgupta et al. 2012a	rs2975760	T	0.72	0.77	*1.36(0.71-2.59)*	*0.34*	Insulin secretion and action
				C	0.28	0.22		**0.41**	
			rs3792267	G	0.9	0.9	*1*	*1*	
				A	0.09	0.09		**0.89**	
			rs2975762	G	0.53	0.49	*0.85(0.48-1.48)*	*0.56*	
				A	0.47	0.51			
			rs3842570	D	**0.54**	**0.54**	*0.96(0.55-1.67)*	*0.88*	
					0.46	0.45		**0.93**	
				I	**0.46**	**0.45**			
					0.54	0.55			
			rs5030952	C	**0.95**	**0.94**	*0.92(0.52-1.61)*	*0.77*	
					0.49	0.47		**0.65**	
				T	**0.04**	**0.05**			
					0.51	0.53			
		Chennai (C2) 169/169 Thangavelu et al.2017	rs2975766	A	0.93	0.96	1.82(0.91-3.66)	0.08	
				G	0.07	0.04			
			rs7607759	A	0.82	0.8	0.87(0.59-1.28)	0.49	
				G	0.18	0.2			
		Hyderabad (H4) 204/204 Thathapudi et al. 2015b	rs3792267	G	0.85	0.81	*0.75(0.35-1.58)*	*0.45*	
				A	0.15	0.19			
12	CDKAL1 (CDK5 regulatory subunit associated protein 1-like 1)	Hyderabad (H1) 248/210 Reddy BM et al. 2016	rs7754840	G	0.76	0.73	0.85(0.63-1.15)	0.29	Development of pancreas and regenerative capacity of pancreatic beta cells
				C	0.24	0.27			
			rs7756992	A	0.73	0.72	0.92(0.69-1.23)	0.58	
				G	0.27	0.28			
13	CDKN2A/B (Cyclin-dependent kinase in hibitor 2A/B)		rs10811661	C	0.15	0.15	0.95(0.66-1.37)	0.75	
				T	0.85	0.85			
14	HHEX(Hematopoietically Expressed Homeobox gene)		rs1111875	A	0.66	0.62	0.84(0.62-1.10)	0.21	Development of pancreas and regenerative capacity of pancreatic beta cells
				G	0.34	0.38			
			rs7923837	A	0.63	0.59	0.84(0.64-1.10)	0.2	
				G	0.37	0.41			

Table 4: Contd...

S. No.	*Gene*	*Population sample size (Case/Control) Reference*	*Studied variants*	*Major/ Minor allele*	*Allele frequency (%)* *Case*	*Control*	*Odds ratio (CI)*	*P value*	*Function*
15	IGF2(Insulin like growth factor 2)	Hyderabad (H4) 204/204 Sujatha et al. 2016	rs680*	A G	0.6 0.4	0.92 0.08	7.63(5.08-11.4)	<0.0001	Stimulates ovarian androgen secretion
16	IGF2BP2 (Insulin growth factor2 mRNA binding protein 2)	Hyderabad (H1) 248/210	rs4402960	G T	0.57 0.43	0.52 0.48	0.82(0.63-1.06)	0.13	Insulin secretion
		Reddy BM et al. 2016	rs1470579	A C	0.56 0.44	0.52 0.48	0.84(0.64-1.08)	0.18	
17	INS (Insulin)	Chennai (C2) 169/169 Thangavelu et al. 2017	rs689	T A	0.88 0.12	0.85 0.14	0.81(0.52-1.31)	0.365	Insulin action and secretion
18	INSL3 (Insulin like 3)	Mumbai (M1) 405/333 Shaikh et al. 2016	rs2286663	G A	0.92 0.08	0.95 0.05	*1.60(0.37-6.82)*	*0.52*	Involves in Androgen production, follicular growth and oocyte maturation
			rs1047233	A G	0.87 0.13	0.9 0.1	*1.34(0.56-3.22)*	*0.5*	
			rs6523	A G	0.56 0.44	0.45 0.55	*0.64(0.36-1.12)*	*0.12*	
			rs1003887	G A	0.51 0.49	0.59 0.4	*1.41(0.80-2.48)*	*0.22*	
19	INSR (Insulin receptor)	Chennai (C2) 169/169 Thangavelu et al. 2017	rs1799817	C T	0.32 0.66	0.33 0.67	0.96(0.69-1.32)	0.806	Insulin action and secretion
		New Delhi (ND2) 50/50 Gangopadhyay et al. 2016	rs1799817*	C T	0.56 0.44	0.28 0.72	*0.30(0.16-0.55)*	*0.0001* **0.008**	
		Mumbai (M1) 180/144 Mukherjee et al. 2009	C/T polymorphism at His1058 in exon 17	C T	*0.69* *0.31*	*0.57* *0.43*	*0.59(0.33-1.06)*	*0.07*	
20	IRS1 (Insulin receptor substrate 1)	Hyderabad (H1) 250/299	rs1801278	G A	0.97 0.03	0.95 0.05	*0.61(0.10-3.29)*	*0.55* **0.32**	Promotes metabolic activities of insulin.
		Dasgupta et al. 2012d	rs2234931	G A	0.96 0.04	0.95 0.05	*0.81(0.16-3.99)*	*0.78* **0.22**	
		Chennai (C2)	rs1801278*	G	0.47	0.57	1.94(1.41-2.66)	<0.001	

Table 4: Contd...

S. No.	*Gene*	*Population sample size (Case/Control) Reference*	*Studied variants*	*Major/ Minor allele*	*Allele frequency (%)* *Case*	*Control*	*Odds ratio (CI)*	*P value*	*Function*
		169/169 Thangavelu et al. 2017		A	0.53	0.43			
21	IRS2 (Insulin recept or substrate 2)	Chennai (C2) 169/169 Thangavelu et al. 2017	rs1805097	G A	0.70/**0.17** 0.3	0.69 0.31	0.95(0.68-1.31)	0.738	
22	PPARγ (Peroxisome proliferator activated recep-tor gamma)	Hyderabad (H1) 250/299 Dasgupta et al. 2012d	rs1801282*	C G	0.88 0.11	0.83 0.16	1.43(0.99-2.05) $	0.05	Glucose and lipid metabolism
			rs3856806*	C T	0.91 0.09	0.87 0.13	1.53(1.02-2.27)$	0.03	
		Hyderabad (H2) 281/299 Deepika et al. 2016	rs1801282	C G	0.91 0.09	0.97 0.03	*3.00(0.60-14.8)*	*0.17* **0.13**	
		Chennai (C2) 169/169 Thangavelu et al. 2017	rs1801282	C G	0.13 0.86	0.14 0.86	1.07(0.69-1.68)	0.73	
			rs3856806	C T	0.85 0.15	0.84 0.16	0.94(0.62-1.41)	0.75	
		Mumbai (M1) 450/300 Shaikh et al. 2013	rs1801282*	C G	0.92 0.08	0.86 0.14	0.55 (0.39–0.77)	0.0004	
			rs3856806*	C T	0.86 0.13	0.82 0.18	0.71(0.53–0.94)	0.01	
		Coimbatore (CM1) 75/75 Raichel et al. 2016	rs1801282	C G	0.88 0.12	0.89 0.1	0.87(0.42-1.79)	0.13	
23	SLC30A8 (Solute carrier (zinc transporter) 30 member 8)	Hyderabad (H1) 248/210 Reddy BM et al. 2016	rs13266634	T C	0.78 0.22	0.78 0.22	0.99(0.72-1.35)	0.94	Insulin secretion
24	TCF7L2 (Transcription factor 7 like 2)	Chennai (C4) 43/43 Prabhu et al. 2018	rs7903146	C T	0.71 0.29	0.71 0.29	0.97(0.73-1.30)	0.84	Blood-Glucose homeostasis
			rs11196205	G C	0.61 0.4	0.63 0.36	0.88(0.66-1.13)$	0.28	
							1.15(0.84-1.58)	0.36	
			rs12255372	G T	0.77 0.23	0.8 0.2			
			rs7903146	T C	—	—	—	No variants found	

Table 4: Contd...

S. No.	*Gene*	*Population sample size (Case/Control) Reference*	*Studied variants*	*Major/ Minor allele*	*Allele frequency (%)* *Case*	*Control*	*Odds ratio (CI)*	*P value*	*Function*
Chronic Inflammatory Pathway Genes									
25	CD14 (Cluster of differentiation 4)	Hyderabad(H6) 219/272 Allauddin and Rozati 2017	rs2569190*	C T	0.63 0.37	0.84 0.16	*3.08 (1.57-6.03)*	*0.001*	Involves in immunologic and inflammatory pathways.
26	Connexin37	Hyderabad (H3) 98/100 Guruvaiah et al. 2016	rs1764391*	C T	0.77 0.22	0.63 0.36	1.98(1.27-3.08)$	0.002	Anti-inflammatory cytokine and is involved in chronic inflammation and atherosclerosis.
27	IL-1β (Interleukin 1 beta)	New Delhi (ND1) 95/45 Nadia et al. 2017	C [-511] T	C T	0.3 0.69	0.33 0.67	*1.13(0.62-2.05)*	*0.682* **0.637**	Mediates inflammatory response, and is involved in cell proliferation, differentiation, and apoptosis
28	IL-1 Ra (Interleukin 1 Receptor antagonist)		VNTR	II III IV V VI	0.26 0.02 0.69 0.01 0.01	0.27 0 0.72 0.01 0	—	0.475	Modulates a variety of interleukin 1 related immune and inflammatory responses.
29	IL-6 gene (Interleukin 6)	Hyderabad (H3) 104/156 Tumu et al. 2013	rs1800795*	G C	0.81 0.19	0.73 0.27	1.62(1.05-2.48)$	0.025	Stimulation of the hypothalamic pituitary adrenal axis and modulation of lipid metabolism.
30	TLR4 (Toll-like receptor 4)	Hyderabad (H6) 219/272 Allauddin and Rozati 2017	rs4986790*	A G	0.61 0.39	0.81 0.19	*2.72 (1.43-5.17)*	*0.002*	Involves in immunologic and inflammatory pathways.

Table 4: Contd...

S. No.	*Gene*	*Population sample size (Case/Control) Reference*	*Studied variants*	*Major/ Minor allele*	*Allele frequency (%)* *Case*	*Control*	*Odds ratio (CI)*	*P value*	*Function*
31	TNF-α (Tumor Necrosi Factor alpha like 1)	Hyderabad(H4) 204/204 Thatapudi et al. 2014	rs1799724*	C T	0.94 0.06	0.72 0.28	0.17(0.11-0.27)	<0.0001	Regulation of immune cells
		Hyderabad(H2) 283/306 Deepika and Ranjith 2013	rs1799964	T C	0.68 0.32	0.76 0.24	0.67(0.36-1.25)$	0.27	
			rs1800629	G A	0.52 0.48	0.51 0.49	1.04(0.59-1.81) $	0.88	
		Rohtak(R1) 200/200 Bhatnager et al. 2018a	rs361525*	G A	*0.74* *0.26*	*0.59* *0.41*	*0.50(0.27-0.92)*	*0.02*	
			rs1800629	G A	*0.6* *0.4*	*0.68* *0.32*	*1.41(0.79-2.53)*	*0.24*	
			rs1799724	C T	*0.6* *0.4*	*0.68* *0.32*	*1.41(0.79-2.53)*	*0.23*	
			rs1800630	C A	*0.64* *0.36*	*0.67*/**0.07** *0.33*	*1.14(0.63-2.04)*	*0.65*	
			rs1799964	T C	*0.76* *0.24*	*0.65* *0.35*	*0.58(0.31-1.08)*	*0.08*	
32	ICAM-1 (Intercellular adhesion molecule 1)	Kashmir(KS1) 220/220 Douhath et al. 2016	rs1799969	Gly (G) Arg (R)	0.65 0.35	0.64 0.36	0.98(0.74-1.29)	0.88	Encodes a glycoprorein which is expressed on endothelial and cells of immune system.
		Kashmir (KS1) 220/220 Douhath et al. 2017	rs5498	Lys (K) Glu (E)	0.63 0.37	0.61 0.39	0.92(0.70-1.20)	0.53	
Obesity Related Genes									
33	ADPIOQ (Adiponectin, C1Q and collagen containing)	Coimbatore and Kerala(CMK) 282/200 Nambiar et al. 2016	rs2241766	T G	0.86 0.14	0.88 0.12	1.17(0.80-1.72)	0.4	Insulin sensitizing adipokine with anti-atherogenic, anti-infla-mmatory and cardio protective properties.
			rs1501299	G T	0.25 0.75	0.29 0.71	1.23(0.92-1.65)	0.14	
34	Leptin	Mumbai(M1) 100/100 Pusalkar et al. 2010	G19A untranslated exon 1	G A	—	—	—	No association	Energy metabolism
		Mumbai(M1) 30/25 Anurupa et al. 2004	exon 2 and 3	—	—	—	—	No variations	

Table 4: Contd...

S. No.	*Gene*	*Population sample size (Case/Control) Reference*	*Studied variants*	*Major/ Minor allele*	*Allele frequency (%)* *Case*	*Control*	*Odds ratio (CI)*	*P value*	*Function*
35	PGC-1α (Peroxisome proliferator activated receptor gamma coacti-vator-1 alpha)	Hyderabad(H3) 118/110 Reddy TV et al. 2018	rs8192678*	G	0.58	0.69	1.60(1.09-2.36)	0.01	Energy metabolism
				A	0.42	0.31			
			rs13131226	T	0.66	0.71	1.24(0.83-1.85)	0.27	
				C	0.34	0.29			
			rs2970856	T	0.75	0.78/**0.29**	1.16(0.75-1.79)	0.27	
				C	0.25	0.22			
36	FABP1 (Fatty Acid Binding Protein 1)	New Delhi (ND1) 95/45 Nadia et al. 2017	rs2197076	A	0.45	0.49	*1.17(0.67-2.04)*	*0.571*	Involves in fatty acid metabolism. Prevents Cytotoxicity
				G	0.55	0.51		**0.546**	
Tumor Suppressor Genes									
37	BRCA1 (Breast cancer 1)	Hyderabad(H3) 110/130 Siddamalla et al. 2018a	rs71361504*	W	0.69	0.58	1.63(1.12-2.39)$	0.009	Tumor suppressor genes
				M	0.31	0.42			
			rs3092986*	T	0.9	0.97	0.26(0.10-0.62) $	0.001	
				C	0.1	0.03			
38	BRCA2 (Breast cancer 2)		rs206118	A	0.81	0.8	1.06(0.67-1.68) $	0.78	
				G	0.19	0.2			
39	TP53 (Tumor protein p53)	Hyderabad (H3) 110/130 Siddamalla et al. 2018a	rs1042522*	G	0.5	0.63	0.59(0.41-0.86) $	0.005	Tumor suppressor gene
				C	0.49	0.36			
Vitamin D Related Genes									
40	VDR (Vitamin D Receptor)	Hyderabad (H1) 250/250 Dasgupta et al. 2015	rs11568820*	G	0.86	0.71	*0.39(0.19-0.81)*	*0.01*	Regulates vitamin D levels and calcium metabolism.
				A	0.14	0.29		**<0.001**	
			rs2228570	C	0.8	0.78	*0.89(0.45-1.73)*	*0.73*	
				T	0.21	0.23		**0.46**	
			rs7975232	C	0.29	0.29	*0.98(0.53-1.81)*	*0.96*	
				A	0.71	0.72		**0.86**	
			rs731236	T	0.63	0.65	*1.06(0.59-1.88)*	*0.84*	
				C	0.37	0.36		**0.58**	
		Hyderabad (H3) 95/130 Siddamalla et al. 2018b	rs1544410*	A	0.6	0.71	0.62(0.41-0.92)$	0.01	
				G	0.39	0.29			
			rs7975232*	A	0.55	0.67	0.60(0.40-0.82) $	0.009	
				C	0.44	0.32			
			rs731236*	T	0.58	0.71	0.58(0.39-0.86) $	0.006	
				C	0.41	0.29			
		Kolkata (K2) 125/82	rs2228570	A	*0.44*	*0.55*	*1.55(0.89-2.71)*	*0.12*	
				G	*0.56*	*0.45*			

Table 4: Contd...

S. No.	*Gene*	*Population sample size (Case/Control) Reference*	*Studied variants*	*Major/ Minor allele*	*Allele frequency (%)* *Case*	*Control*	*Odds ratio (CI)*	*P value*	*Function*
		Dipanshu and Ratnabali 2015	rs7975232	A C	*0.46* *0.54*	*0.57* *0.43*	*1.55(0.89-2.71)*	*0.12*	
			rs2282679	T G	*0.56* *0.44*	*0.62* *0.38*	*1.28(0.72-2.25)*	*0.38*	
			rs12785878	T G	*0.58* *0.42*	*0.65* *0.35*	*1.34(0.75-2.38)*	*0.39*	
41	VDBP (Vitamin D Binding Protein)	New Delhi (ND2) 50/50 Haldar et al. 2018	rs7041	T G	*0.52* *0.48*	*0.47* *0.53*	*0.81(0.46-1.42)*	*0.47*	Vitamin D transport
			rs4588	C A	*0.68* *0.32*	*0.7* *0.3*	*1.09(0.60-1.98)*	*0.75*	
42	CYP2R1 (Cytochrome P450 Family 2 Subfamily R	Member 1)	rs2060793	A G	*0.53* *0.47*	*0.54* *0.46*	*1.04(0.59-1.81)*	*0.88*	Involves in hydroxylation
Other Candidate Genes									
43	ACE (Angiotensin I converting enzyme)	Hyderabad (H2) 259/315 Deepika et al. 2013	I/D	D I	0.57 0.43	0.57 0.43	Cases did not follow HWE	1	Regulates blood pressure, fluid balance and ovarian function
44	Mitochondrial D-loop region	Hyderabad(H3) 118/114 Reddy TV et al. 2019	D310*	—	0.54	0.28	—	0.04	May participate in the organization of mitochondrial nucleoid
			A189G*	—	0.26	0.13	—	0.01	
45	MTHFR Methylene tetrahydrofolate reductase	Indo-Europeans, Dravidians (CV) 261/256 Carlus et al. 2016	rs1801133 (677C>T)	C T	—	—	1.11(0.71-0.72)	0.66	Processing amino acids
		Varnasi(V1) 92/97 Jain et al. 2012	C677T	C T	0.91 0.08	0.93 0.06	1.29(0.60-2.77)	0.5	
46	PAI-1 (Plasminogen Activator Inhibitor 1)	Chennai(C1) 30/30 Mary et al. 2017	rs1799889	4G 5G	0.5 0.5	0.43 0.57	1.30(0.63-2.68)$	0.46	Involves in extracellular matrix remodeling and fibrinolysis

Table 4: Contd...

S. No.	*Gene*	*Population sample size (Case/Control) Reference*	*Studied variants*	*Major/ Minor allele*	*Allele frequency (%)* *Case*	*Control*	*Odds ratio (CI)*	*P value*	*Function*
47	PON1 (Paraoxonase 1)	Mumbai(M1) 516/424 Dadachanji et al. 2018	Promoter region						Anti-atherosclerotic component of HDL
			108C/T	C	0.61	0.57	*0.82(0.46-1.45)*	*0.5*	
				T	0.38	0.43		**0.079**	
			162G/A	G	0.72	0.72	*1*	0.82	
				A	0.28	0.28			
			824G/A	G	0.6	0.62	*1.08(0.61-1.92)*	*0.77*	
				A	0.4	0.38		**0.35**	
			907G/C	G	0.62	0.57	*0.79(0.44-1.39)*	*0.41*	
				C	0.37	0.43		**0.01**	
			1076A/G	A	0.71	0.71	*1*	0.96	
				G	0.29	0.29			
			126G/C	G	-	-	-	-	
				C					
			-24C/T	Novel mutation		-	-	-	-
		Mumbai(M1) 482/326 Dadachanji et al. 2015	L55M	lean					
				L	0.85	0.74	*0.52(0.25-1.06)*	*0.07*	
				M	0.15	0.25		**0.009**	
				obese					
			Q192R	L	0.84	0.85	*1.07(0.50-2.32)*	*0.84*	
				M	0.16	0.15		**0.7**	
				Lean					
				Q	0.58	0.63	*1.26(0.71-2.24)*	*0.41*	
				R	0.42	0.36		**0.24**	
				obese					
				Q	0.58	0.61	*1.13(0.64-1.99)*	*0.66*	
				R	0.42	0.39		**0.45**	
48	PEPD (Prolidase/ Peptidase D)	Rohtak(R1) 200/200 Bhatnager et al. 2018b	rs267606943	C	0.75	0.77	*1.11(0.58-2.14)*	*0.74*	Provides instructions for prolidase which helps in the breakdown of collagens.
				T	0.25	0.23		**0.67**	

Table 4: Contd...

S. No.	*Gene*	*Population sample size (Case/Control) Reference*	*Studied variants*	*Major/ Minor allele*	*Allele frequency (%)* *Case*	*Control*	*Odds ratio (CI)*	*P value*	*Function*
49	RETN (Resistin)	Coimbatore and Kerala(CMK) 282/200 Nambiar et al. 2016	rs1862513*	C G	0.43 0.57	0.14 0.86	0.27(0.19-0.38)	0.0001	May modulate molecular pathways involved in metabolic, inflammatory and autoimmune diseases.
			rs3745368	G A	0.68 0.32	0.66 0.34	0.92(0.70-1.21)	0.58	
			rs3745367*	G A	0.29 071	0.81 0.19	1.81(1.32-2.46)	0.001	
50	TFAM (Mitochondrial transcription factor A)	Hyderabad (H3) 118/110 Reddy TV et al. 2018	rs1937	G C	0.85 0.15	0.90 0.09	0.60(0.96-3.31)$	0.08	Regulates mitochondrial transcription
51	VEGF (Vascular Endothelial Growth Factor)	Hyderabad(H3) 126/130 Guruvaiah et al. 2014	+405G/C *	G C	0.74 0.26	0.63 0.37	1.67(1.15-2.44)$	0.006	Promotes angiogenesis and vascular permeability
			-406C/T	T C	0.55 0.45	0.53 0.47	1.08(0.76-1.53) $	0.63	

*-significant SNPs; $-odds ratio calculated with respect to major allele; Number in bold is computational error and the corrected value included; values in italics are odds ratios calculated by the present authors from the given allele/genotypic frequencies by using R software.

Table 5: The relative percentage of PCOS genes from different pathways studied in India

S. No.	Pathway	Genes studied		Variants studied	
		No.	*(%)*	*No.*	*(%)*
1	Reproductive pathway genes	11	(21.15%)	20	(19.23%)
2	Type 2 Diabetes genes	14	(26.92%)	32	(30.77%)
3	Chronic inflammatory pathway genes	8	(15.38%)	12	(11.54%)
4	Obesity related genes	4	(7.69%)	6	(5.76%)
5	Tumor suppressor genes	3	(5.76%)	4	(3.85%)
6	Vitamin D related genes	3	(5.76%)	10	(9.61%)
7	Other candidate genes	9	(17.30%)	20	(19.23%)
	Total	52		104	

Reproductive Pathway Genes

Hyperandrogenism is one of the key characteristic manifestations of PCOS and the genes related to steroidogenesis like CYP1A1, CYP11A1, CYP17A1 and CYP19A1 have been studied for their association with the syndrome. The CYP1A1 gene polymorphism-rs6235, (Table 4) were explored in two population samples, from Hyderabad-H5 (Babu et al. 2004) and Varanasi-V1 (Jain et al. 2015) and found to be not significantly associated with PCOS. While the CYP11A1 repeat polymorphism was associated with PCOS in the Hyderabad-H2 sample (Reddy KR et al. 2014) and confers risk, the penta nucleotide polymorphism in the promoter region and the exons 3, 4 and 9 of this gene were not associated with PCOS in the Mumbai-M1 sample (Anurupa et al. 2004), which was too small (30) to accord any statistical power. The rs743572 of CYP17A1 in Amritsar-A1 sample (Kaur et al. 2018) and C/T polymorphism in the promoter region of the same gene in Kolkata-K1sample (Banerjee et al. 2016) were not associated with PCOS. Further, the M1 study investigated promoter region polymorphisms of CYP11A1 and CYP17A1 genes and observed significantly higher means of the testosterone levels in PCOS cases than controls (Pusalkar et al. 2009). On the other hand, the allelic association of three SNPs of CYP19A1- rs700519, rs2414096 and rs6027 1534- in H2 sample (Ranjith et al. 2015) and two of the above three SNPs- rs700519 and rs2414096- in Amritsar-A1 sample were not significant. Furthermore, sequencing all the exons of FST gene in the H1 sample of Hyderabad, while Dasgupta et al. (2012c) found no variants, of the seven variants of LH β gene in the same sample only rs1056917-C was found to be significant with risk conferring nature towards PCOS (Dasgupta et al. 2012b). Also, the rs2293275-G of LHCGR gene was found to be significant with risk for PCOS in the H4 sample of Hyderabad (Thathapudi et al. 2015a).Three variants of FSHR in C3 sample (Kambalchenu et al. 2014) and one variant, rs6166-G which is common to C3 was explored in H4 sample (Thathapudi et al. 2016) and found to be significant only in the latter with protective nature. Further, of the two variants of HSD11B1 gene studied in Mangalore-MN1sample, only rs12086634-G was found to be associated with risk for PCOS (Devang et al. 2018).The variant rs6259 of SHBG gene was not associated with PCOS in Rohtak-R1 sample (Bhatnager et al. 2019). A review and meta-analysis of a few variants of SHBG gene suggested that the lower serum SHBG levels were associated with PCOS risk (Deswal et al. 2017).

Metabolic Pathway Genes

PCOS is also associated with several metabolic co-morbidities like insulin resistance, obesity, T2DM, CVDs and metabolic syndrome. Therefore, genes related to T2DM, obesity, coronary diseases have been explored. A significant association of obesity rather than raised testosterone with dyslipidemia in PCOS women was observed in a North Indian study (Maitra et al. 2001). Given that Asian Indians are insulin resistant and prone to metabolic syndrome at an earlier age, Sundararaman et al. (2003) investigated glucose/insulin ratio and IMT (intimal median thickness) and observed that South Indian women with reproductive abnormalities of PCOS have greater insulin resistance and IMT. The incidence of diabetes is high in India and therefore this feature was considered in few studies of India. The prevalence of polycystic ovaries was found to be higher in diabetic subjects

as compared to the non-diabetic subjects in North Indian women (Zargar et al. 2005). Insulin resistance is also associated with dyslipidemia in PCOS women, which was independent of obesity (Kalra et al. 2006). Further, the status of molecular events underlying insulin resistance and the contribution of insulin signaling pathway genes in the pathogenesis of PCOS was reviewed by Mukherjee and Maitra (2010).

a. T2DM Related Genes

Given the shared pathophysiology of PCOS and diabetes, both these conditions demonstrate insulin resistance and compensatory hyperinsulinemia. The diabetic perspective of PCOS was assessed by Reddy BM et al. (2016) considering 15 T2DM related SNPs belonging to genes like INS, INSR, HHEX, TCF7L2, INSL3 and SLC30A8 in the population of Hyderabad-H1 but failed to find significant association. The same sample was also explored earlier for certain SNPs of CAPN10, IRS1 and PPARγ (Dasgupta et al. 2012a, 2012d) and the Chennai-C2 study (Thangavelu et al. 2017) subsequently investigated variants belonging to CAPN10, INS, INSR, IRS1 and IRS2. The variant rs7903146 of TCF7L2, which was already explored in H1 study did not show any association even in the C4 sample (Prabhu et al. 2018).The five variants of CAPN10-rs2975760, rs3792267, rs2975762, rs3842570 and rs5030952 in H1 population, one variant rs3792267 in H4 which was restudied (Thathapudi et al. 2015b) and the two more variants-rs2975766 and rs7607759 explored in C2 were not significantly associated with PCOS. The INSR variant rs1799817-T was studied in C2 as well as in the New Delhi-ND2 population (Gangopadhyay et al. 2016) and was found to be significantly associated only in the ND2 population albeit with protective nature towards PCOS. Further, the C/T polymorphism in the exon 17 of INSR gene was not associated with PCOS in Mumbai-M1 sample (Mukherjee et al. 2009). The variant rs1801278-A of IRS1 was studied in H1 (Dasgupta et al. 2012d) and C2 populations and found to be associated with risk conferring nature towards PCOS only in the C2 sample from Chennai.

The rs680-G of IGF2 gene in H4 sample (Sujatha et al. 2016) was significantly associated with much higher risk for PCOS. Further, the INS variant-rs689 and IRS2 variant-rs1805097 in C2 and 4 variants of INSL3- rs2286663, rs1047233, rs6523 and rs1003887 studied in M1 sample (Shaikh et al. 2016) were not associated with PCOS. Five studies have explored the variants of PPARγ in the H1, H2, C2, M1 and Coimbatore-CM1 samples (Dasgupta et al. 2012d; Shaikh et al. 2013; Deepika et al. 2016; Raichel et al. 2016; Thangavelu et al. 2017). Interestingly, rs1801282-G was studied in all populations and rs3856806-T studied in H1, C2 and M1 populations. Both SNPs were found to be significantly associated with PCOS but protective in nature in the H1 and M1 samples.

b. Chronic Inflammatory Pathway Genes

PCOS is a pro-inflammatory state disease and genes related to chronic inflammation might contribute to the manifestation of PCOS via an inter-mediatory role among hyperandrogenism, obesity, insulin resistance and anovulation (Ojeda-Ojeda et al. 2013). Therefore, genes like CD14, TLR4, IL-1β, IL-1Ra, IL-6, TNF–α and ICAM-1 were investigated. The variants rs2569190-T of CD14 and rs4986790-G of TLR4 gene were found to be associated with significant risk in the H6 sample (Allauddin and Rozati 2017). While the variants rs1764391-T of Connexin 37 and rs1800795-C of IL-6 were found to be associated with PCOS in H3 sample (Tumu et al. 2013; Guruvaiah et al. 2016), rs1799724-T of TNF–α was associated in H4 sample (Thathapudi et al. 2014), albeit protective in nature. However, the variants TNF–α (rs1799964 and rs1800629) in H2 study (Deepika and Ranjith 2013) and those of IL-1β and IL-1Ra in ND1 sample (Nadia et al. 2017) were not associated with PCOS. Nevertheless, Deepika et al. (2016) in the H2 sample explored the association of rs1801282 of PPARγ and rs1799964 of TNF–α with BMI in PCOS and revealed that the over-expression of PPARγ in the absence or lower levels of TNF–α increases PCOS risk. Further, of the five variants of TNF- α explored in R1 sample three were restudied in the H2 and H4 samples, and only rs361525-A was found to be associated with protective nature for PCOS in the R1 sample (Bhatnager et al. 2018a). The variants of ICAM-1 gene, rs1799969 and rs5498, were not associated with PCOS in Kashmir-K1 population (Douhath et al. 2016; 2017).

c. Obesity Related Genes

Very few studies in India have explored the association of obesity related genes with PCOS.

Two variants of ADIPOQ gene -rs2241766 and rs1501299- were not associated with PCOS in the mixed Coimbatore and Kerala samples-CMK (Nambiar et al. 2016). The rs2197076 of FABP1 gene which affects hepatic lipid accumulation and results in altered lipid metabolism (Xue et al. 2015) was studied in ND1 population and was not found to be associated with PCOS (Nadia et al. 2017). The exons 1, 2 and 3 of Leptin gene were screened in M1 population but no association was observed (Anurupa et al. 2004; Pusalkar et al. 2010). However, irrespective of the obesity status, leptin levels were higher in PCOS cases indicating that increased BMI/obesity may not be the only factor contributing to elevated levels of Leptin. Overall, the results suggest that androgen and leptin levels are increased in PCOS and obesity. It demonstrates that obesity is a confounding factor for hyperandrogenaemia irrespective of their PCOS status. The H3 study explored 3 variants of PGC-1α- rs8192678, rs1313226 and rs2970856, of which rs8192678-A was found to be associated with risk conferring nature towards PCOS (Reddy TV et al. 2018).

d. Tumor Suppressor Genes

Tumor suppressor genes- BRCA1, BRCA2 and TP53 were explored for their association with PCOS in H3 population (Siddamalla et al. 2018a). While the rs71361504 (mutant) as non-risk and rs3092986-C as risk conferring variants of BRCA1 were found to be significantly associated with PCOS, the rs206118 of BRCA2 was not. The rs1042522-C of TP53 was also found to be significantly associated as risk conferring variant for PCOS in this population.

e. Vitamin D Related Genes

The Vitamin D receptor (VDR) regulates vitamin D levels and calcium metabolism in the body and these are associated with endocrine dysfunctions, insulin resistance and type 2 diabetes in PCOS. The genetic studies on VDR polymorphisms in PCOS women are sparse (Dasgupta and Reddy 2008). The three studies- H1 (Dasgupta et al. 2015), H3 (Siddamalla et al. 2018b) and K2 (Dipanshu and Ratnabali 2015) have explored seven variants of which only the rs7975232-C was explored in all the three samples and found to be associated as risk variant only in H3 study. Likewise the rs731236-C studied in H1 and H3 samples was associated only in H3 sample with risk for PCOS but rs2228570 explored in H1 and K2 was not associated. However, the rs11568820-A (non-risk) in H1 and rs1544410-G (risk) in H3 were associated with PCOS. A review and meta-analysis of some of the VDR gene variants showed FOK1 polymorphism as a risk factor for PCOS (Deswal et al. 2018). Further, the rs7041 and rs4588 of VDBP gene and rs2060793 of CYP2R1 gene were not found to be associated with PCOS in ND2 population (Haldar et al. 2018).

Other Candidate Genes

The mitochondrial D-loop region was investigated in H3 population and among 19 polymorphisms tested for their association with PCOS, only 2 were found to be significant (Reddy TV et al. 2019). The TFAM polymorphism-rs1937 (Reddy TV et al. 2018) and two polymorphisms of VEGF gene (Guruvaiah et al. 2014) were also explored in the same sample from Hyderabad and only one of those at +405 G>C 5' untranslated region of VEGF gene was found to be associated as protective towards PCOS. The variant rs1801133 of MTHFR gene, which is involved in amino acid processing was examined in mixed samples of Chennai and Varanasi- CV (Carlus et al. 2016) and in a sample of V1 populations (Jain et al. 2012) but was not found to be significant. Further, a meta- analysis of CV study sample with others of Caucasians, Asians and Turkish origin also supported the lack of association of this variant with PCOS. A novel mutation (-24C/T) in the promoter region of PON1 gene which is an antioxidant and is involved in many metabolic diseases (Turgut et al. 2016) was reported in 6 PCOS and 3 control samples in M1 study (Dadachanji et al. 2018) but these authors could not find association of two SNPs of PON1 with PCOS in an earlier study (Dadachanji et al. 2015). The ACE gene I/D polymorphism in H2 (Deepika et al. 2013), PAI-1 SNP, rs1799889, in C1 sample (Mary et al. 2017) and the rs267606943 of PEPD gene studied in R1 sample (Bhatnager et al. 2018b) were also not associated with PCOS. Further, three variants of RETN gene were explored in the mixed sample of Coimbatore and Kerala-CMK, of which rs1862513-G was associated with risk and rs3745367-A in protective roles towards PCOS (Nambiar et al. 2016).

CONCLUSION

Given the enormous ethnic, geographic and linguistic heterogeneity of the Indian populations and that these populations possibly show different patterns of genetic susceptibility to complex diseases when compared to other ethnic groups, the genetic studies hitherto conducted are too few and too inadequately represented the Indian population in order to depict Indian specific susceptibility profile of the PCOS women in general. All together only 23 different samples were studied from 11 major cities of India, more than 70 percent of which were repeat samples from five cities: Hyderabad (6: H1- H6), Chennai (5: C1- C4, CV),Coimbatore (2: CM1,CMK), Kolkata (2: K1, K2) and New Delhi (2: ND1and ND2). The variation in sample sizes is too large and within Mumbai sampling unit (M1), the sample size for different studies varied from 30 to 516 cases. With reference to studies from New Delhi (ND1, ND2), Kolkata (K1), Varanasi (V1), Chennai (C1,C4) , Coimbatore (CM1) and Hyderabad (H3), in particular, the sample sizes were too small (30 to 98) to accord sufficient statistical power to these studies. However, most of the Indian studies used Rotterdam criteria-2003 in recruiting PCOS cases except for one study group in Hyderabad-H3 which used Androgen Excess Society (AES) - 2006 criteria.

A relatively greater number of diabetes pathway genes were studied followed by those of reproductive pathway when compared to other pathways. Also, relatively much wider spectrum of variants belonging to different pathways was explored in the population of Hyderabad when compared to the other regions. Overall, only 29 of the 104 variants studied in different populations were found to be associated with PCOS ($p \leq 0.05$), eighteen of those being risk prone. Further, these variants appear to be very modestly associated and confer only minor effects and therefore not causative, which is in congruence with the general scenario hitherto observed. Further, there was inconsistency in the association of few SNPs belonging to FSHR, PPARγ, INSR, TNF-α and VDR genes that were screened in more than one sample. The rs6166 of FSHR that was associated in H4 was not found to be significant in C4 sample. The PPARγ- rs1801282, associated with PCOS in H1 and M1 samples, was not found significant in H2, CM1 and C2 studies. Similarly, rs3856896 was associated in H1 and M1 and not associated in C2 study. The INSR -rs17999817 associated in ND2 was not significantly associated with PCOS in C2 study. Also, the TNF-α-rs1799724 was not associated in R1 but was observed to be significant in H4 study. Further, the variants of VDR gene studied in two samples of Hyderabad- H1 and H3- and in one of the two samples from Kolkata (K2) were associated with PCOS only in H3. This kind of inconsistent results can be expected primarily due to sampling and/or genotypic errors, albeit the role of vastly different allelic frequencies between the populations concerned cannot be also ruled out. Most of the significantly associated SNPs of PCOS in India have not been replicated in another sample/population of India. Also the genetic studies explored only few SNPs belonging to same gene or different genes and entire gene was not considered. We could also observe computational errors in the statistical analysis of the genotypic data in a number of studies.

RECOMMENDATIONS

Although multiple genes, environmental factors and their interactions play a role in the manifestation of PCOS none of the studies hitherto investigated the role of environmental factors rigorously, which needs to be the focus of future studies. In view of the phenotypic heterogeneity of this syndrome, it may be also pertinent to turn focus toward phenotype specific genetic investigations to offset the problems associated with confounding nature of the samples with mixed phenotypes. Further, given the unique population structure and genetic susceptibility patterns of Indians, it is essential to conduct large scale studies encompassing ethnic and geographic heterogeneity of the country so that a representative genetic susceptibility profile of the Indian PCOS women in general can be derived. There has also been no GWAS on Indian specific PCOS samples and it would be imperative to conduct multiple GWAS in order to unearth the unique susceptibility profile of the Indian PCOS women, if exists.

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APPENDIX

Table 1: Clinical studies on PCOS in India along with the salient features of their findings. The reference numbers under the table correspond to the serial numbers of different studies

S. No.	*Studies*	*Important findings*
1	Multidimensional relationship of mood pathology with endocrine disturbances was examined.	Higher prevalence of PCOS is observed.
2	Clinical, biochemical and metabolic parameters among different PCOS phenotypes and controls were compared.	PCOS women with Phenotype A (oligo/anovulation/ +/ hyperandrogenism/ +/ polycystic ovaries) and B (/ oligo/anovulation +/ hyperandrogenism) lie at increased metabolic risk compared to other phenotypes.
3	Correlations between anthropometric parameters and lipid profile in women with PCOS.	BMI and Waist Circumference are the most important anthropometric parameters correlated to dyslipidemia.
4	The role of Obesity in sleep-disordered breathing women with polycystic ovary syndrome was examined.	Testosterone-induced obesity is probably the common pathway for the development of sleep disordered breathing in PCOS.
5	The serum metabolomic profile of Indian women with PCOS and controls was investigated.	Dysregulations in the expression of different metabolites in the serum of women with PCOS suggesting the involvement of multiple pathways including amino acid metabolism, carbohydrate/lipid metabolism, purine and pyrimidine metabolism and protein synthesis.
6	The carotid intimo medial wall thickness (CIMT) of PCOS was compared with controls.	Higher CIMT values were observed in PCOS group compared to control group indicating the importance for measuring CIMT in women with PCOS to predict the risk of cardiovascular dysfunction (CVD).
7	The impact of serum 25OHD (25 hydroxy vitamins) levels on clinical, biochemical and insulin sensitivity parameters in the lean Indian women with PCOS was assessed.	No significant correlation was observed.
8	The alterations in the levels of plasma amino acids in women with PCOS was assessed.	Significant derangement in the levels of plasma amino acids in women with PCOS was observed which might be due to the oxidative and metabolic stress associated with it.
9	To estimate the prevalence of abnormal glucose tolerance (AGT) and analyze the role of oral glucose tolerance test.	AGT was found to be high among young Indian women with PCOS and that it is not predicted by family history of type 2 Diabetes Mellitus. OGTT (Oral Glucose Tolerance Test) significantly improves the detection rate of AGT among Indian women with PCOS.
10	Parameters like thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), tetraiodothyronine (FT4), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein cholesterol (VLDL-C) homocysteine (HCY), lipoprotein(a) (Lp[a]) levels were assessed.	Alteration in lipid metabolism and elevated HCY and Lp(a) levels were present in women with PCOS, which were independent of their thyroid status.
11	CVD risk in young women with PCOS using CIMT and brachial artery flow mediated dilation (FMD) which are markers of subclinical atherosclerosis was assessed.	Young women with PCOS irrespective of their BMI have evidence for increased CVD risk as shown by increased CIMT and a lower FMD.
12	Clinical features of PCOS in Indian women were studied to characterize different phenotypes of this syndrome. Prevalence of acanthosis nigricans (AN) as surrogate marker of insulin resistance, obesity, hirsutism and hypothyroidism in PCOS women have been simultaneously studied.	PCOS occurs both in obese and non-obese women; AN and hirsutism occur in equal proportion of patients AN is correlated with obesity. Hormonal dysfunctions in PCOS manifested together or independently. PCOS women can be sub grouped based on clinical features suggestive of endocrinological malfunctions and can be investigated accordingly for selection of appropriate treatment modalities.
13	Association of Graves disease and PCOS.	The association of a rare disorder like Graves' disease with a relatively common disorder like PCOS is unlikely to be because of a chance alone and may point

Table 1: Contd...

S. No	*Studies*	*Important findings*
		to a common aetiopathogenic linkage leaving a scope for molecular characterization.
14	To evaluate the presence of microalbuminuria in women with PCOS and study its correlation with the various metabolic, clinical, and hormonal parameters.	Screening for the presence of microalbuminuria can help in early identification of a subset of PCOS women with a high risk for future cardio vascular disease, who can be subjected to preventive strategies at the earliest.
15	Psychological aspects of women with PCOS.	Women presenting with PCOS had increased psychological distress, which was related to smaller size of family, and more severe physical manifestations of the condition.
16	The relationship between insulin resistance and abdominal fat distribution was studied in Indian patients with PCOS.	Subcutaneous fat, together with a family history of type 2 diabetes mellitus, was the best marker of insulin resistance.
17	To study the correlation between insulin resistance and serum lipid profile in Indian women with PCOS.	Insulin resistance is associated with dyslipidemia in women with PCOS, independent of obesity.
18	The prevalence of PCO and PCOS in women with diet and/or oral hypoglycemic treated T2DM and non-diabetic control women.	A higher prevalence of PCO in women with T2DM as compared to non-diabetic subjects was demonstrated.
19	Dsyslipidemia in PCOS women with particular emphasis on specific parameters of atherosclerotic risk, and to assess the independent influence of obesity and hyperandrogenemia on these parameters.	Confirms the trend toward dyslipidemia among women with PCOS, particularly in parameters associated with cardiovascular risk. A significant association of obesity rather than raised testosterone with this dyslipidemia was also confirmed.
20	The different patterns of glucose and insulin secretion in women (of both Indian and white ethnic backgrounds) with PCOS was determined.	The ethnic background of subjects with PCOS needs to be considered in studies on the metabolic parameters in this condition.
21	The prevalence of anxiety and depression among women suffering from PCOS was studied.	Infertility and alopecia were associated with anxiety, while acne was associated with depression. Hirsutism was associated with a lower psychological quality of life.
22	The independent attributes of hyperandrogenemia (HA), the integral associate of PCOS, and HHcy (hyperhomocysteinemia) in causing atherogenic dyslipidemia was investigated.	HA may independently attribute to an increased cardiovascular risk in PCOS; however, the coexistence of HHcy catalyzes the risk further.
23	To evaluate the oxidant status and hsCRP (high sensitive C-reactive protein) levels in PCOS.	Oxidative stress is present in women with PCOS along with elevated hsCRP.
24	Identification of differentially regulated proteins in PCOS by comparing the follicular fluid protein repertoire of PCOS with healthy women.	Proteins indispensable for follicular growth were found to be differentially expressed in follicular fluid of women with PCOS, which may in part explain the aberrant folliculogenesis observed in these women.
25	The anthropometric, biochemical and ultrasonographic characteristics of PCOS in Asian Indians of South India, using the Androgen Excess Society (AES-2006) diagnostic criteria was investigated.	Significant differences were observed among PCOS subgroups. The PCOS subgroups with regular menstrual cycles (HA+PCO), had high insulin resistance (IR) and gonadotropic hormonal abnormalities, compared with the irregular menustration+ hyperandrogenism+polycystic ovaries subgroups and controls.
26	The correlation between serum adiponectin levels and clinical characteristics and biochemical parameters in PCOS patients was assessed.	Hypoadiponectinemia is present in one-fifth of women with PCOS. Adiponectin levels decrease as age advances. Low levels of adiponectin possibly contribute to the development of dermal manifestation (AN) of insulin resistance.
27	The prevalence of clinical manifestations in obese and lean polycystic ovarian syndrome (PCOS) women and their health hazards was evaluated.	PCOS emerges as a clinically heterogeneous condition with increased prevalence of health risks such as hypertension, diabetes and endometrial hyperplasia (EH). Of these, diabetes and EH appear to be more prevalent in the obese, putting them at a greater risk of morbid problems at a much younger age than the lean ones.

Table 1: Contd...

S. No	*Studies*	*Important findings*
28	The role of hypothyroidism in the etiology of PCOS was explored.	Comparative analysis of the results suggests that hypothyroidism is invariably followed by a lowering of sex hormone binding globulin and an increment in the free testosterone level, but further metabolism of testosterone (T) may or may not be directed towards an overproduction of estriol (E3).
29	The correlation between serum adiponectin levels and clinical characteristics and biochemical parameters in PCOS patients was studied.	Hypoadiponectinemia is present in one-fifth of women with PCOS. Adiponectin levels decrease as age advances. Low levels of adiponectin possibly contribute to the development of dermal manifestation (acanthosis nigricans) of insulin resistance.
30	To obtain evidence for the genetic basis of polycy stic ovaries (PCO) and premature male pattern baldness (PMPB) by screening first-degree relatives of women affected by polycystic ovary syndrome (PCOS).	The inheritance of PCO and PMPB is consistent with an autosomal dominant inheritance pattern in PCOS families, perhaps caused by the same gene. Men with PMPB had higher serum testosterone than those without. A spectrum of clinical phenotype in PCOS families was observed.
31	To assess the prevalence of hirsutism and study its etiology in the Kashmir Valley of the Indian subcontinent.	Hirsutism is as common a problem in the Kashmir Valley (India) as elsewhere in the world. Idiopathic hirsutism (38.7%), PCOS (37.3%), and postmenopausal state (9.2%) are common causes of hirsutism.
32	To study the correlation between insulin resistance and serum lipid profile in Indian women with PCOS.	Insulin resistance is associated with dyslipidemia in women with PCOS, independent of obesity.
33	To find out the prevalence of metabolic syndrome (MBS) in women with PCOS and assess their strength of association.	The metabolic syndrome and its individual components are common in PCOS, particularly among women with hyperinsulinemia and hyperandrogenism.
34	Correlation between serum lipid profile and carotid intima-media thickness in PCOS was examined.	Carotid intima-media thickness was positively correlated with serum total cholesterol, triglyceride and LDL-C and negatively correlated with serum HDL-C.This study suggests that even young Polycystic Ovary Syndrome women are prone to atherosclerosis from early age.
35	To establish the relation between PCOS and metabolic syndrome in Karnataka.	An incidence of 38% of metabolic syndrome was noted in PCOS cases.
36	To evaluate the prevalence of metabolic syndrome in women with polycystic ovary syndrome.	Infertile women with PCOS, particularly those with age $\geq$25 years or with central obesity (a waist hip ratio of $\geq$0.85), are at a higher risk of developing metabolic syndrome and should be offered screening tests.

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