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3 **A study on the pattern of genetic inheritance of**

4 **polycystic ovarian syndrome**

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**Aims:** Inheritance of polycystic ovary syndrome (PCOS) is still a controversy. Our study aims to analyze the family history of PCOS features and related metabolic disturbances including the male members to determine the mode of their inheritance.

**Study design:** A cross sectional study with convenient sampling.

**Place and Duration of Study:** Department of Medicine, Kasturba Medical College, Mangalore between 2009 and 2012.

**Methodology:** Demographic data such as body weight and age was recorded. Menstrual, obstetric and medical history of 85 PCOS females was collected. Presence of metabolic syndrome (MetS) was confirmed. Blood pressure and waist circumference were measured. Biochemical and hormonal estimations were done. Relevant information required for the study of 604 members of first and second generation relatives was collected. SPSS (version 17.0) was used to analyze the data.

**Results:** Seventy eight percent of the PCOS patients were either overweight or obese and 98% of them had hirsutism. Approximately, 33% of them had MetS which was higher in the first generation (62%) of PCOS relatives. An equal transmission of MetS characteristics from the paternal and maternal side indicated that it was not X-linked inheritance. Segregation analysis of nine families PCOS of patients suggested that MetS inheritance was autosomal dominant although PCOS inheritance was not.

**Conclusion:** PCOS daughters come from families of MetS suggesting that parental MetS features may be related to the occurrence of PCOS in their off-springs.

**Key words:** *Polycystic ovary syndrome, Obesity, Metabolic syndrome, Inheritance*

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9 **1. INTRODUCTION**

10 Polycystic ovary syndrome (PCOS) affects 5-10 % of the women in reproductive age group.

11 An increase in the prevalence of PCOS among Indians is also a great concern. Estimates of

12 PCOS in migrant Indians have been placed at 52% level and about 37% among the north

13 Indian women have been reported to suffer from PCOS [1,2]. Gynecologists from South

14 India believe from their experience that 25-30% of the women visiting them do suffer from

15 PCOS. However, a recent report puts the figure at 9.13% [3].

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18 Genetic factors play an important role in the development of PCOS, but studies in this regard

19 in India is scanty. Maitra *et al* [4]. conducted mutational analysis of CPY1A1 and leptin as

20 genetic determinants of hyperandrogenicity and obesity in PCOS. A recent study has clearly  
21 demonstrated the heritable aspects of obesity and insulin resistance in PCOS even in  
22 infancy and also in the male progeny [5,6]. However, studies showing familial clustering of  
23 PCOS cases, greater concordance of symptoms of PCOS in identical twins, heritability of  
24 endocrine and metabolic features of PCOS are all compelling evidences that strongly  
25 suggest the involvement of genetic mechanism [7]. Although, search for candidate genes in  
26 PCOS has yielded some positive results, the controversy on the mode of inheritance (eg.  
27 autosomal dominance, modified autosomal dominance, X-linked, polygenic, oligogenic or  
28 multifactorial) still persists [8]. Therefore, we propose this study on the family history of  
29 PCOS subjects at length including male members, not only for PCOS but also for its related  
30 metabolic conditions to determine the pattern of inheritance of PCOS.

## 31 32 **2. MATERIAL AND METHODS**

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34 By convenient sampling, 85 post-pubertal female subjects, preferably with a large family  
35 size, diagnosed with PCOS were inducted for the study. Institute's research ethical  
36 committee approved the study. Written consent was obtained from each of the 85  
37 participants who were given a clear explanation of the purpose of the study. The diagnosis of  
38 PCOS was made according to the ESHRE/ASRM criteria based on the presence of two of  
39 the three following criteria: oligo- and/or anovulation (menstrual dysfunction), clinical and/or  
40 biochemical signs of hyperandrogenism and polycystic ovaries (PCO) at ultrasonogram [9].

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42 All patients were questioned in detail regarding birth history, menstrual, obstetric and  
43 medical history. Medical history of diabetes mellitus, hypertension, cardiovascular diseases,  
44 dyslipidemia and malignancies of breast/ovary/endometrium and thyroid disorders were  
45 recorded. Also, a standard questionnaire was used to document personal history such as  
46 troublesome acne, excess sweating, excess body hair (hirsutism), male pattern hair loss,  
47 acanthosis nigricans, buffalo hump and goiter.

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49 As a routine, *in vitro* tests for direct quantitative determination of fasting blood sugar (FBS),  
50 postprandial blood sugar (PPBS), total cholesterol (TC), triglyceride (TG) and high density  
51 lipoprotein (HDL-C) was carried out on Roche-Hitachi fully automated random access  
52 chemistry analyser (RH model P-800). Relevant hormones evaluation was conducted by  
53 Electrochemiluminescence immunoassay (ECLIA) on Cobase 411 modular immunoassay  
54 analyser. However, we are not providing any results or discussing this part of the data as it  
55 is not relevant for this communication.

56  
57 Prevalence of metabolic syndrome (MetS) was also assessed by ATP-III standards [10,11].  
58 Accordingly, MetS was diagnosed in subjects presenting with at least three of five of the  
59 following criteria: increased waist circumference (>80 cm), low serum HDL-C (<50 mg/dl in  
60 women), increased serum TG (>150 mg/dl), increased blood pressure (>130/>85 mm Hg)  
61 and high FBS (>100 mg/dl).

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63 Relevant data of six hundred and four (604) family members of the PCOS patients was  
64 gathered from all 85 PCOS patients for analysis of the pattern of inheritance of PCOS. They  
65 were questioned for PCOS conditions and related MetS features in their first and second  
66 degree relatives and the information was recorded.

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68 A statistical software package was used to analyse the numerical data (SPSS version 17.0).  
69 Univariate analysis was done by using one-way ANOVA and *Kruskal-Wallis test* (non-  
70 parametric).  $P < 0.05$  was considered statistically significant. The results are expressed as  
71 Mean  $\pm$  SD. Segregation analysis was carried out to determine the inheritance of PCOS.

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73 **3. RESULTS**

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75 The mean age of the PCOS subjects in this study was 27.9±7.1 years. The average age of  
76 onset of menarche was 12.8±1.5 years. Body mass index (BMI) based grouping (for Asians)  
77 of the PCOS patients is shown in Table 1 along with blood pressure and waist circumference  
78 data. It was obvious that 34%, 44% and a very small group of the subjects were in  
79 overweight, obese and underweight categories, respectively.

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82 **Table1. Body mass index (BMI), waist circumference (WC) and blood pressure (BP) of**  
83 **subjects grouped on BMI basis.**

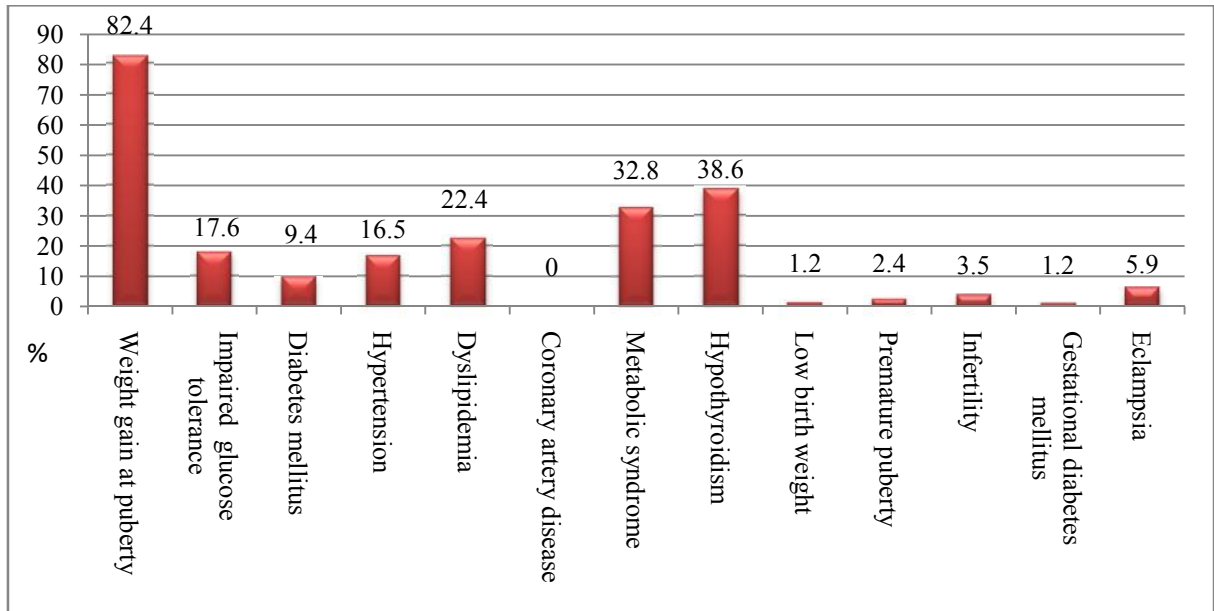
<b>BMI Range</b>	<b>n</b>	<b>%</b>	<b>BMI (Kg/m<sup>2</sup>)</b>	<b>WC (cm)</b>	<b>Systolic BP (mmHg)</b>	<b>Diastolic BP (mmHg)</b>
<18.5 (Underweight)	3	3.5	17.0 ±0.8	63.7±8.0	110.0±17.3	66.7±11.5
18.5-22.9 (Normal)	16	19	20.9 ±1.4	75.4±8.8	126.2±6.1	79.3±7.7
23-27.4 (Overweight)	29	34	25.6 ±1.4	81.4±6.5	124.4±9.8	78.2±6.0
27.5-34.9 (Obese I)	32	38	30.6 ±1.8	90.0±9.4	133.0±12.7	83.1±8.5
>35 (Obese II)	5	6	38.9 ±4.1	111.2±19.9	140.0±20.0	88.0±8.3
				p< 0.000	p< 0.001	p< 0.001

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86 Figure 1 represents certain clinical conditions suffered by the PCOS patients. More than 1/3  
87 of the patients had shown hypothyroidism and MetS features and a considerable number of  
88 them had diabetes mellitus, hypertension and dyslipidemia. More than 80% of the subjects  
89 had gained extra body weight at puberty.

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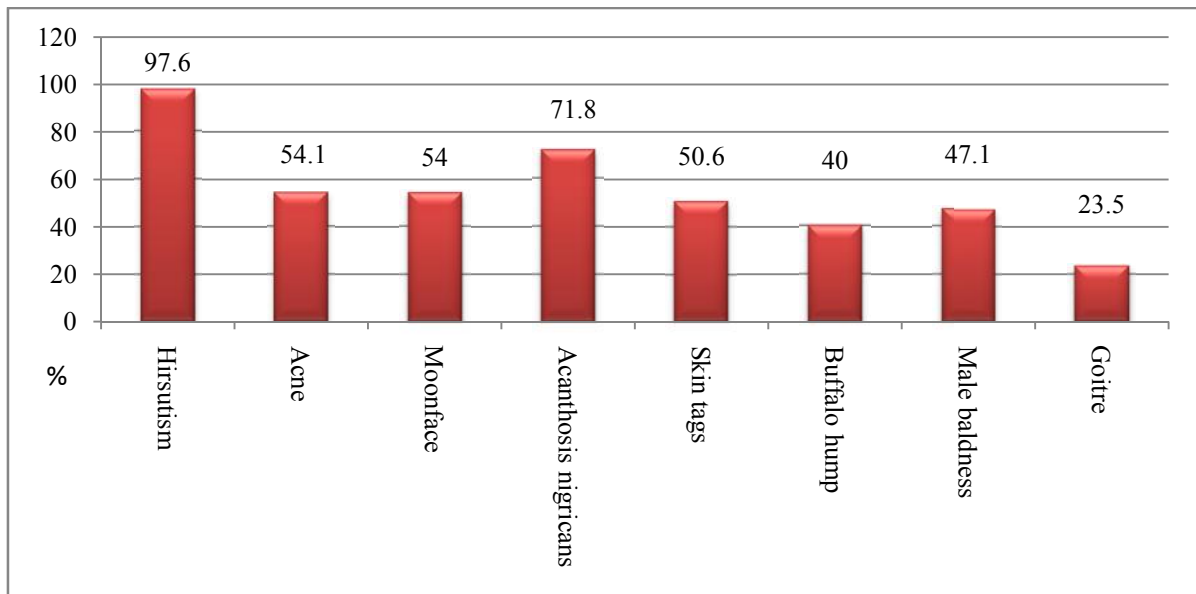
92 **Figure1. Clinical conditions (%) associated with the PCOS patients**

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94 Figure 2 shows the clinical features of 85 PCOS patients where 98% of them had hirsutism,  
 95 a characteristic of clinical hyperandrogenemia resulting in PCOS.

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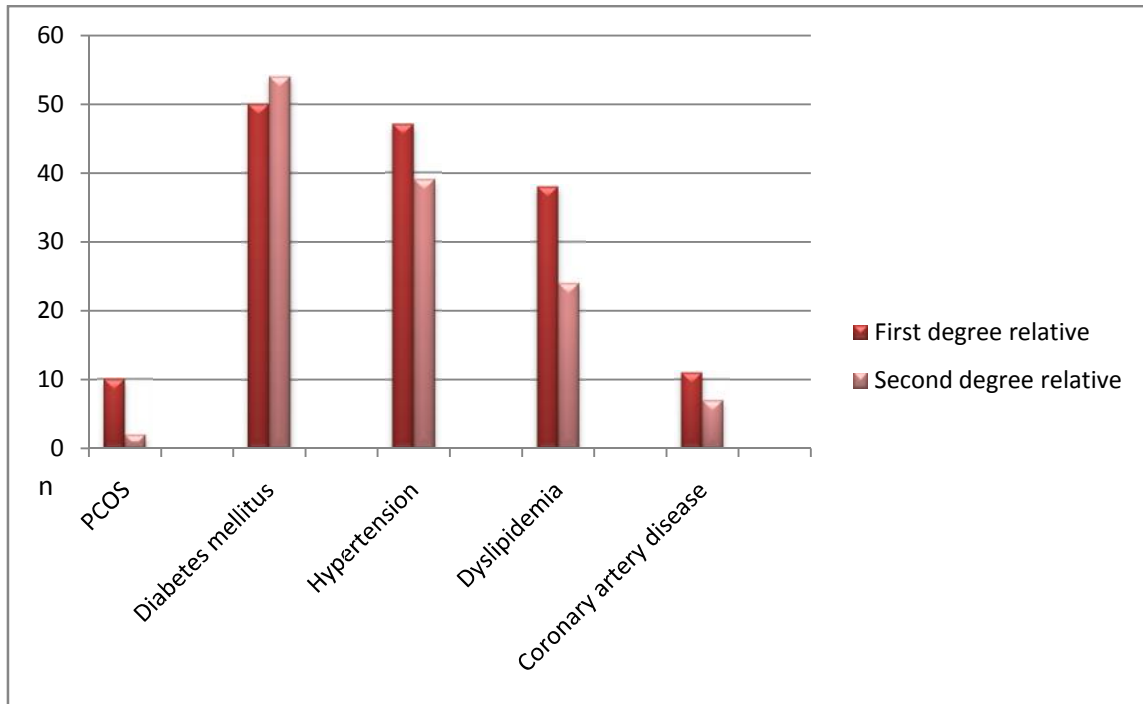
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100 **Figure 2. Clinical features (%) of the PCOS patients.**

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Figure 3 depicts the prevalence of PCOS and related MetS characteristics and coronary artery disease (%) in the first and second degree relatives of the PCOS patients in this study. The prevalence of all the conditions (except diabetes mellitus) were relatively less (statistically significant except for diabetes mellitus and coronary artery disease) in second degree relatives as compared to the first.



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110 **Figure 3. Frequency of clinical conditions (%) in first and second degree relatives of**  
111 **PCOS patients.**

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Table 2 shows the presence of some clinical conditions in the relatives of the PCOS subjects in detail as reported by them.

129 **Table 2. Distribution of polycystic ovary syndrome (PCOS) patients' relatives with of**  
 130 **some clinical conditions; CAD = coronary artery disease.**  
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PCOS patients' relatives	n	Diabetes mellitus	Hypertension	Dyslipidemia/ Obesity	CAD	PCOS
		n (%)	n (%)	n (%)	n (%)	
Father	65	23 (35.4)	23 (35.4)	14 (21.6)	7 (10.8)	-
Mother	65	20 (30.8)	18 (27.7)	13 (20.0)	2 (3.1)	5
Brother	57	4 (7.0)	3 (5.3)	3 (5.3)	2 (3.5)	-
Sister	49	3 (6.1)	3 (6.1)	8 (16.3)	-	5
Father's Brother	28	15 (53.6)	5 (17.9)	7 (25.0)	3 (10.7)	-
Father's Sister	25	5 (20.0)	5 (20.0)	5 (20.0)	-	-
Mother's Brother	21	8 (38.1)	4 (19.0)	1 (4.8)	1 (4.8)	-
Mother's Sister	34	9 (26.5)	6 (17.4)	8 (23.5)	1 (2.9)	-
Grand Father (P)	65	3 (4.6)	6 (9.2)	1 (1.5)	1 (1.5)	-
Grand Mother(P)	65	4 (6.2)	3 (4.6)	-	-	-
Grand Father (M)	65	4 (6.2)	3 (4.6)	1 (1.5)	1 (1.5)	-
Grand Mother(M)	65	6 (9.2)	7 (10.8)	1 (1.5)	-	-

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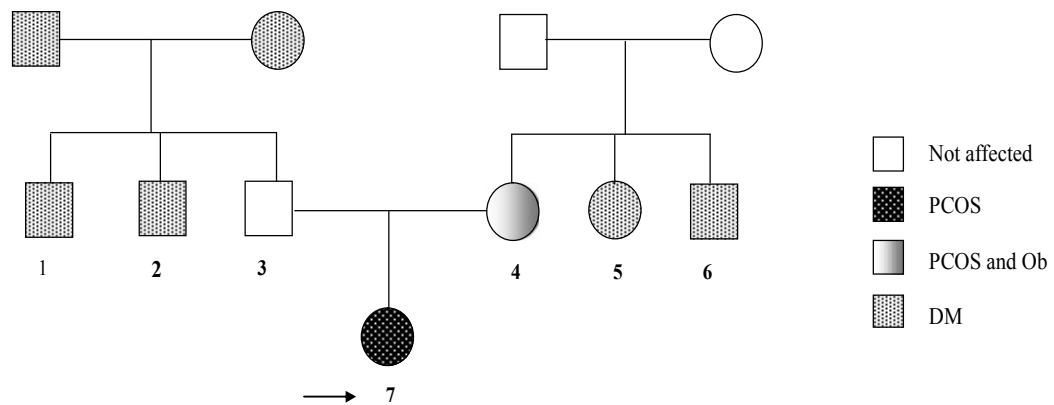
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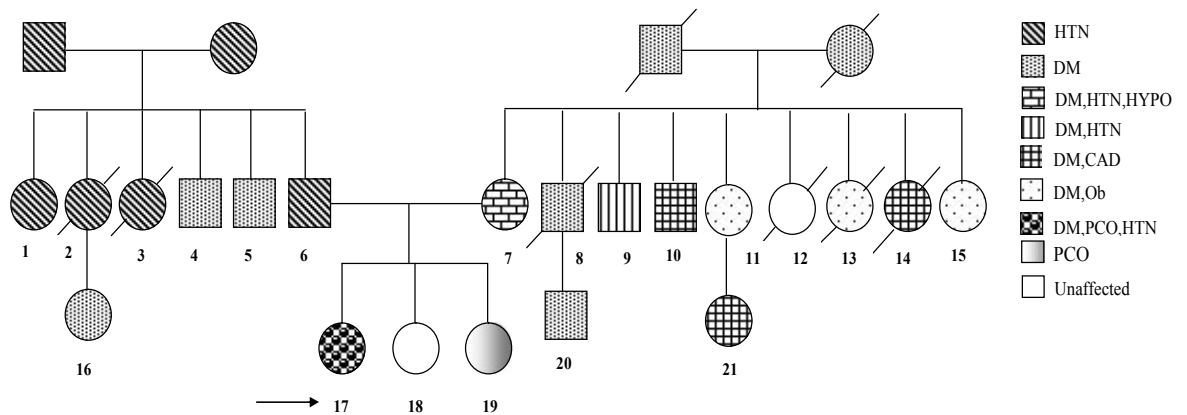
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Family pedigree analysis of 9 PCOS subjects with large families in our study showed that the mothers of three PCOS probands had PCOS. We also found PCOS in the siblings of three of the PCOS subjects with no history of PCOS in their mothers. Moreover, we also found MetS features being present in the parents and in most of the second degree family members in three of the PCOS probands who had one or more associated MetS characteristics at an early age. The segregation ratio (observed:expected) was consistent with autosomal dominant inheritance in all these cases. Figures 4a and 4b represents a sample of the pedigree tree of two of our PCOS patients.



**Figure 4a.** The proband 7 in this family had polycystic ovary syndrome (PCOS). The proband's mother 4 had PCOS and obesity (Ob). Proband's paternal uncle (1) and maternal aunt (5) had diabetes mellitus (DM). Paternal grandparents had DM.

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**Figure 4 b.** In this large family, the proband 17 had polycystic ovary (PCO), obesity (Ob), hypertension (HTN) and infertility (INF). One of her sisters (19) had PCO and Ob. The proband's mother (7) suffered from diabetes mellitus (DM), HTN and hypothyroidism (HYPO) and father (6) had HTN. DM was found in three maternal uncles (8,9,10) and three maternal aunts (11,13,15) of the proband. All maternal aunts were obese and two of them (11,12) were dead due to breast carcinoma. Proband's maternal grandparents had DM and paternal grandparents suffered from HTN. Three paternal aunts (1,2,3) had HTN and two paternal uncles (4,5) had DM. The off-springs of paternal aunt and maternal uncle (16, 21) also had features of metabolic syndrome (MetS).

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#### 150 4. DISCUSSION

151 PCOS has become a 'family affair'. Susceptibility to inheritance of PCOS seems to be  
152 equally probable from both the maternal and paternal side of the family. It is estimated that a  
153 woman's risk for developing PCOS is higher, if she has an affected sister, but at a lower risk,  
154 if other family members are affected [12]. Though, the genetic studies have not yet  
155 determined the pattern of heredity, most of the family studies have shown a simple  
156 Mendelian pattern of inheritance consistent with an autosomal dominant or X-linked pattern  
157 of inheritance [13]. Positive findings have been reported with candidate genes involved in  
158 both association and linkage studies [14]. However, twin studies on PCOS have revealed an  
159 incidence of 50% that suggest a complex pattern of polygenic inheritance [15]. On the other  
160 hand, a large family study (St Mary's family) from Franks' group concluded that PCOS is  
161 inherited on an oligogenic basis [16].

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163 The high incidence of PCOS in first degree relatives of the PCOS affected members in some  
164 studies [13,15,17-18]. suggests a dominant pattern of inheritance based on the assumption  
165 that at least 50% of the siblings of the PCOS probands are affected with the disorder [13]. A  
166 few studies over the last 20 years have drawn attention to the phenomenon of familial  
167 clustering of PCOS cases [19-23]. In some of these studies, segregation analysis gave  
168 results that were consistent with autosomal dominant inheritance [19,22-23]. In one study by  
169 Govind *et al.*, that included 29 families of PCOS probands, segregation analysis showed that  
170 52% of the mothers, 21% of the fathers, 66% of the sisters and 22% of brothers were  
171 affected with PCOS features that supported an autosomal dominant inheritance pattern of  
172 PCOS in families, perhaps caused by the same gene [13]. In another study, the prevalence  
173 of polycystic ovaries among siblings was too high to be explained by a simple dominant  
174 model [21]. Legro *et al.*, studied 80 PCOS probands and reported that 36 of 80 (45%) sisters  
175 were affected on the basis of hyperandrogenemia [24]. Another study has reported a  
176 prevalence of 50% hirsutism cases among the affected sisters of PCOS [17]. They also have  
177 shown that some characteristics of PCOS inherited were in different proportion; e.g. PCO  
178 73%, hyperandrogenemia 87% and hyperinsulinemia 66%. A report by Givens *et al.*, has  
179 suggested an X-linked mode [20]. Wilroy *et al.*, showed that 47% of female offspring of  
180 PCOS patients in their study were affected. Among the offspring of males with an elevated  
181 LH/FSH ratio, 89% of daughters were affected [25]. The finding is thus consistent with X-  
182 linked dominant inheritance.

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184 Natasha *et al* [26] have tested the hypotheses that parental MetS would be related to the  
185 PCOS phenotype in their offspring and that MetS prevalence would be increased in  
186 adolescents with PCOS. Thirty-six adolescent girls with PCOS and their first degree relatives  
187 were evaluated for MetS characteristics in their study concluded that familial factors related  
188 to paternal MetS seem to be fundamental to the pathogenesis of PCOS.

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190 A recent study from south India on 432 individuals comprising of 206 patients and 226  
191 controls has revealed a high frequency of PCOS women exhibiting family history of  
192 menstrual disturbance, type II diabetes and cardiovascular diseases in their families as  
193 compared to the control families thus showing a familial clustering [27]. Such familial history  
194 of complex diseases can be the most informative risk factors for the development PCOS.  
195 Similarly, our study revealed that a total of 10 members from the families of 85 PCOS  
196 probands, referred to as first generation and two members from the second generation had  
197 PCOS features. We also diagnosed MetS in nearly one third of them. However, when we  
198 analyzed MetS characteristics associated with PCOS, we found a very high association  
199 suggesting autosomal dominant transmission. Break up data of the family history showed



200 nearly 20% of the fathers and 20% of mothers of PCOS probands having diabetes mellitus,  
201 hypertension obesity/dyslipidemia each. Among the siblings of PCOS probands, nearly 10%  
202 of them had diabetes mellitus, hypertension, and obesity/dyslipidemia. However, among the  
203 uncles, aunts and grandparents of our PCOS probands, the percentage of diabetes mellitus,  
204 hypertension, and obesity/dyslipidemia was less than 10%. When any one of the MetS  
205 features such as diabetes mellitus , hypertension or dyslipidemia was considered, we found  
206 a prevalence of 62% (146/236) and 33% (124/368) among the first degree and second  
207 degree relatives of our PCOS subjects respectively. This proves the autosomal dominant  
208 inheritance of the MetS features in PCOS.

## 209 210 **5. CONCLUSION**

211 In summary, PCOS is one of the most controversial entities for many years and has been  
212 proven to be a familial condition in gynecological endocrinology with features of chronic  
213 anovulation and hyperandrogenism [28]. Although, there is strong support for the role of  
214 genes and the environmental contributions involved in the etiology of the syndrome, they  
215 have not been either fully investigated or the reports are contradictory [28, 29, 30].  
216 Moreover, no gene or genes is universally accepted as important in the pathogenesis of  
217 PCOS, though the numbers of candidate genes are steadily increasing since the problems in  
218 genetic studies of PCOS are manifold [15,31,32]. The current view supports the notion that  
219 PCOS is likely to represent a complex oligogenic trait with multiple genetic defects [33].  
220 Despite these shortcomings, the study of familial aggregates has consistently suggested that  
221 the mode of inheritance to be dominant.

222  
223 In our study there was an equal transmission of MetS characteristics from the paternal and  
224 maternal side indicating that it is not X- linked inheritance. Although, our results do not  
225 demonstrate the autosomal dominant pattern of inheritance of PCOS, the first degree  
226 relatives of the PCOS probands had metabolic characteristics indicating autosomal pattern  
227 of inheritance, suggesting that parental MetS features may be related to their off-springs.  
228 Such manifestations may be influenced by age, diet and environmental factors. In this  
229 context, the suggestion that PCOS should be treated as a quantitative trait disorder which  
230 does not necessarily imply a truly polygenic aetiology because it would be possible to  
231 explain the variable phenotype on the basis of a small number of key causative genes (a so-  
232 called oligogenic basis for disease) involved in androgen secretion and insulin  
233 secretion/action in conjunction with environmental, particularly nutritional factors should be  
234 noted [34].

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