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Heritability and the risk of developing androgen excess ☆

Melissa Kashar-Miller [a, b], Ricardo Azziz [b, c,*]

[a] Laboratory of Medical Genetics, The University of Alabama at Birmingham, Birmingham, AL, USA
[b] Departments of Obstetrics and Gynecology, The University of Alabama at Birmingham, Birmingham, AL, USA
[c] Departments of Medicine, The University of Alabama at Birmingham, Birmingham, AL, USA

Abstract

Androgen excess is one of the most common reproductive endocrinologic abnormalities of women. Excluding specific etiologies such as androgen-secreting neoplasms and non-classic adrenal hyperplasia, the majority of androgen excess is functional in nature. It is clear that studies concerned with the heritability of this disorder greatly depend on how it is defined. Patients with the PolyCystic Ovary Syndrome (PCOS) are clearly included. However, we argue that ovulatory women with hirsutism and hyperandrogenemia should also be considered as affected which, together with PCOS, comprise the population of women we define as having Functional Androgen Excess (FAE). Our data, and that of others, suggests that FAE/PCOS is a familial disorder, with a single autosomal dominant gene effect and a variable phenotype. Inheritance appears to be equally probable from the maternal as from the paternal side of the family. Nonetheless, our data also suggests that the affection rate among mothers is less than expected, which may be due to decreased fertility of affected mothers, or to our inability to detect the disorder in older, menopausal or hormonally treated individuals. Finally, it appears that a woman's risk for developing PCOS is approximately 40% if her sister is affected. While considering FAE/PCOS to be a dominant genetic disorder with a high degree of expressivity, its highly variable phenotype suggests that besides a single genetic mutation other factors must be contributing to the development and expression of the disorder. These factors may include environmental influences (such as fat and carbohydrate consumption) exercise level, peripubertal stress and/or hormonal exposure; and additional genetic defects, such as those that regulate insulin secretion or determine body type.

1. Introduction

Androgen excess is a common reproductive endocrinologic disorder of women, in which the levels and/or the action of androgens is above normal. There are multiple causes of androgen excess [1], including androgen-secreting adrenal or ovarian tumors and 21-hydroxylase (21-OH) deficient Non-Classic Adrenal Hyperplasia (NCAH). However, the vast majority of androgen excess is of functional nature, i.e. non-neoplastic and not arising from a well defined genetic defect. A number of investigators have reported that the development of the disorder is under significant genetic control, although the mode of transmission is unclear. Following we explore the definition and classification of Functional Androgen Excess (FAE), describe potential inheritance modes and report on our recent findings regarding its clinical heritability.

1.1. Definition and classification of functional androgen excess

An accurate definition of the disorder under consideration is critical for the development of any related genetic study. It has been difficult to establish a concrete, widely accepted definition of FAE due to the extreme variability of the phenotype. In fact, unclear diagnostic criteria has made interpretation of FAE genetic research difficult. The definition of FAE depends to a great extent on which and how many cri-

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* Corresponding author. Tel.: +1-205-934-5708; fax: +1-205-975-5732.

E-mail address: razziz@uabmc.edu (R. Azziz)

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Phenotypes of Androgen Excess

Features \ Phenotypes	A	B	C	D	E	F	G	H
Ovulatory dysfunction	Y	Y	Y	N	N	Y	N	N
Hyper-androgenemia	Y	Y	N	Y	N	N	Y	N
Hirsutism	Y	N	Y	Y	Y	N	N	N
	PCOS			IH?	IH	Oligo	Nl?	Nl
	FAE				IH	Oligo	Normal	

Fig. 1. Eight different phenotypes are possible if three clinical features are considered to determine the presence or absence of functional androgen excess (FAE). Note that the number of possible phenotypes = X^2-1; where X = number of features considered. Abbreviations: PCOS is the polycystic ovary syndrome, IH is idiopathic hirsutism, Oligo is non-androgenic oligo-ovulation, Nl is normal.

teria or features we use to define the syndrome. For example, let as consider that FAE is defined by the presence or absence of three clinical criteria, i.e., (a) ovulatory dysfunction, (b) peripheral hyperandrogenism (e.g. hirsutism) and (c) hyperandrogenemia. The number of possible phenotypes is then, eight (Fig. 1). Phenotypes G and H are women who are 'normal', albeit group G has elevated androgens and may be considered as outliers in the laboratory. Women with phenotype F have oligo-ovulation unrelated to androgen excess. Phenotypes A-C are considered to represent patients with the Polycystic Ovary Syndrome (PCOS). This phenotypic definition of PCOS is consistent with the criteria arising from a preliminary consensus conference sponsored by the NICHD in April of 1990 [2]. It was concluded 'that the major research criteria for [PCOS] should include (in order of importance); (i) hyperandrogenism and/or hyperandrogenemia, (ii) oligo-ovulation, [and] (iii) exclusion of other known disorders, such as Cushing's syndrome, hyperprolactinemia, or congenital [non-classic] adrenal hyperplasia' [2]. The presence of 'polycystic ovaries on ultrasound', a classic inclusion criterion for many genetic studies, was felt to be 'particularly controversial' as diagnostic for PCOS.

The greatest degree of controversy surrounds the classification of phenotypes D and E (Fig. 1). Some investigators [3–5] have classified patients with regular menstruation and hirsutism as having Idiopathic Hirsutism (IH), regardless of androgen levels. Alternatively, we have argued that the hirsutism is not 'idiopathic' if the excess hair growth arises consequent to an excess in circulating androgens [6]. While the underlying etiology of the excess androgen production may be unknown, the immediate cause of the hirsutism (i.e., hyperandrogenemia) is not. Hence, we define patients as having IH only when they are hirsute, normo-ovulatory and euandrogenic (i.e. phenotype E). This is not merely a semantic issue, as the proportion of androgenized individuals which may be misclassified is significant. For example, in a recent study of 132 hirsute women we noted that 12% demonstrated normo-ovulation and hyperandrogenemia, while another 17% had normo-ovulation and euandrogenemia, the latter group those we would consider as truly having IH [6]. Also of interest was the observation that 40% of patients claiming to have 'regular menstrual cycles' were actually oligo-ovulatory when evaluated more carefully, making the diagnosis of IH according to menstrual history highly inaccurate.

It is possible that women with hirsutism, normo-ovulation and hyperandrogenemia (i.e. phenotype D) represent patients with a mild form of PCOS or who are in the early developmental stages of the disorder. This latter hypothesis, however, is not supported by our finding that women with hirsutism, normo-ovulation and hyperandrogenemia were of similar age to those women with typical PCOS [6]. Regardless, we prefer to consider patients with hirsutism, normo-ovulation and hyperandrogenemia (phenotype D in Fig. 1) as forming part of the PCOS continuum and as also having FAE, along with phenotypes A–C. Overall, the number of women in the general population affected by FAE is significant. In a recent study of 277 unselected women (containing approximately equal numbers of Black and White women) who presented for a pre-employment physical, 4% (11/277) had PCOS and a similar number (12/277) had hirsutism, hyperandrogenemia and regular menstrual cycles [7]. These data would suggest that approximately 8% of the general reproductive-aged population suffers from FAE.

It should be noted that the number of phenotypes to be considered when defining a disorder is directly a function of the number of features considered to form part of the disorder. In essence the number of phenotypes possible is equal to X^2-1, where X is the number of features considered. For example, if we were to add 'polycystic ovaries' as determined ultrasonographically to our criteria for FAE, then the number of phenotypes which should be considered would be 15. Hence, this concept would argue against increasing the number of features to be considered as diagnostic of FAE (or PCOS).

1.2. Review: Clinical studies of the inheritance and genetics of FAE

Following we discuss previous and current investigations on the genetics underlying FAE, or more commonly PCOS. Note that the only difference between patients with PCOS and those with FAE is the inclusion of those patients with hirsutism, hyperandrogenemia but with regular ovulation (or less accurately regular menstrual cycles) into the latter group (see above)—approximately 15–20% of the total.

Table 1
Summary of clinical genetic studies[a]

	Number of probands	Criteria for probands	Method of data acquisition	Controls	Males relatives	Proposed inheritance pattern
Cooper et al., 1968 [8]	18	"Stein-Leventhal Syndrome"	Clinical examination	Random matched	Excessive hairiness	Autosomal dominant
Lorenzo et al., 1970 [9]	90	Hirsutism	Limited clinical examination	Random	Not studied	Multifactorial
Wilroy et al., 1971 [10]	Not pairs stated —48 sibling	PCOS (diagnosed histologically)	Family member interview	None	Not studied	X-Linked dominant
Ferriman et al., 1979 [11]	434	Hirsutism and/or oligomenorrhea	Proband interview	Family of healthy women	PMPB	Modified autosomal dominant
Hague et al., 1988 [12]	61	PCOS	Clinical exam & U/S	None	Not studied	Dominant
Lunde et al., 1989 [13]	132	PCOS	Proband questionnaire	Family of healthy women	PMPB and/or excessive hairiness	Autosomal dominant
Carey et al., 1993 [14]	10	PCOS	Clinical exam & U/S	None	PMPB	Autosomal dominant with full penetrance
Jahanfar et al, 1995 [15]	34 twin pairs	PCOS	Clinical exam & U/S	None	Not studied	Multifactorial or X-linked

[a] Abbreviations: PMPB, premature male pattern baldness; PCOS, the polycystic ovary syndrome; U/S, ultrasound.

The primary investigations on the clinical genetics of PCOS are summarized in Table 1. In 1968, the first multiple family study of the inheritance of PCOS was conducted by Cooper and colleagues at the University of Minnesota [8]. Eighteen probands were selected who had a diagnosis of 'Stein-Leventhal syndrome' based on medical history, physical examination, laboratory data and pathology reports. Only 13 mothers and 24 sisters of patients were actually examined. Matched controls for each family member were carefully selected on the basis of sex, age, race and marital status. In this small study population, a history of oligomenorrhea was more prevalent among mothers and sisters of patients than among controls (31% and 31% vs 0% and 15%, respectively, $P < 0.05$–0.0006). While hirsutism among sisters of patients was more prevalent than among controls (58% vs 29%, respectively, $P < 0.032$), the difference between mothers and their controls did not reach statistical significance (31% vs 15%, respectively, $P = 0.322$). An autosomal dominant mode transmission was proposed.

Lorenzo reported on 90 hirsute probands, and was one of the few studies in which the inclusion criteria did not require the presence of 'polycystic-appearing' ovaries [9]. A limited physical examination was conducted on willing mothers and sisters which included only an evaluation of the face for excess hair, acne, or frontal balding. Three hundred untreated controls were picked at random from a community health study population, and underwent a full assessment of hirsutism and other androgenic equivalents. This study suggested an increased prevalence of hirsutism among the female relatives and acne and/or frontal balding among the male relatives of the probands when compared to controls. A multifactorial inheritance was proposed.

In 1971, Wilroy and colleagues reported a family study of PCOS which was the first to include the proband's aunts [10]. Probands were selected based on the histopathologic diagnosis of PCOS, although their clinical features were not reported. A total of 48 sibling pairs with 150 family members were queried for complaints of oligomenorrhea and hirsutism. In the families apparently exhibiting maternal inheritance ($n = 28$, or 58%), 39 out of 93 female members complained of oligomenorrhea and/or hirsutism with a segregation ratio of 0.47. In the 15 sibling pairs suggesting paternal inheritance (31%), 41 out of the 47 female relatives reported to be affected, with a segregation ratio of 0.87. The segregation ratio was 0.90 (i.e., 9/10 affected female relatives) for families who appeared to have combined maternal and paternal inheritance ($n = 5$, 10%). An X-linked dominant mode of inheritance was proposed, although male relatives were not evaluated. Furthermore, no controls were included.

Ferriman and Purdie published the largest family study of FAE to date, including 434 probands with oligomenorrhea and/or hirsutism [11]. As controls, 179 women were recruited, who did not suffer from hirsutism, oligomenorrhea or infertility. Unfortunately, data on the proband's mothers, fathers and sisters were obtained only through proband interview, and were not confirmed clinically or by family member interview. A modified autosomal dominant mode of inheritance was proposed for hirsute and nonhirsute patients.

Hague and colleagues reported on 50 patients with PCOS. In addition, 17 women with either Classic Adrenal Hyperplasia (CAH) or NCAH were added to the study population [12]. The incidence of 'polycystic-appearing' ovaries among their female relatives was studied, and if at least one female relative demonstrated this pattern the disorder was considered to be familial. Unfortunately, the investigators combined the families with adrenal hyperplasia, a disorder with clear autosomal recessive inheritance, and those with PCOS for analysis. The segregation ratios differed significantly from those predicted for both autosomal dominant and X-linked inheritance.

In 1989, a Norwegian study reported on the prevalence of the clinical manifestations among relatives of 132 patients with PCOS [13]. Data on relatives was obtained only by having the probands complete a mail-in questionnaire, comparing the family history obtained to that of 71 healthy controls. If the data for all 132 families was combined, neither an autosomal dominant nor an X-linked dominant inheritance could be detected. Alternatively, if only the subset of 52 families in which either the mother or the father demonstrated signs of androgen excess was analyzed, an autosomal dominant mode of transmission was suggested.

The most comprehensive family study on the inheritance of PCOS was reported by Carey and colleagues [14]. Fourteen patients diagnosed with 'polycystic' ovaries by ultrasound were recruited into the study. All first degree relatives were contacted, and ten families were identified with sufficient family members available to complete the study. A total of 89 relatives were screened. Blood samples were obtained and analyzed for gonadotrophins, testosterone, prolactin and 17α-hydroxyprogesterone by radioimmunoassay. Unfortunately, a control population was not included in this study. Female relatives were assessed for the presence hirsutism and acne, and a history of irregular menstrual cycles, and underwent transabdominal ultrasonography. Thirty-seven out of the 50 (74%) female relatives who completed screening were observed to have 'polycystic' ovaries on ultrasound, and 31 of these 37 (84%) demonstrated clinical indicators (e.g. hirsutism, acne and/or irregular menses) of androgen excess. Furthermore, 31 of 32 female relatives with irregular menses and/or hirsutism had 'polycystic' ovaries. In 54% of the female relatives with 'polycystic' ovaries, serum levels of LH, testosterone, or both, were elevated. In addition, 22 male relatives were screened for a potential male marker, i.e. Premature Male Pattern Baldness (PMPB), defined in this study as significant frontal-parietal hair loss before the age of 30 years. Of the 18 men who were old enough to be evaluated, eight (44%) demonstrated PMPB. However, no biochemical abnormalities in these men were noted. Male and female first, second and third degree relatives from the ten kindreds were determined to be affected, unaffected or of unknown status based on screening results and histories. Excluding the probands, a segregation ratio of 51.4% was calculated, which is consistent with an autosomal dominant mode of inheritance with almost full penetrance.

Finally, Jahanfar and colleagues studied 19 monozygotic and 15 dizygotic twin pairs, and used ultrasound to detect PCOS [15]. In this study the investigators did not find evidence that PCOS detected sonographically was determined by a single autosomal gene defect. The investigators suggested that PCOS resulted from the influence of combined genetic and environmental factors, or from a sex-linked disorder associated with non-random X-chromosome inactivation.

The family studies described above suggest that FAE/PCOS may be an inherited disorder. However, most of these studies are limited in that they lack some important components, including:

1. *Restrictive diagnostic criteria:* A principal draw-back of many family studies is the restrictiveness of their diagnostic criteria. Many of the studies recruit probands, and determine affected status among relatives, using ovarian morphology—not endocrine—criteria. Nonetheless, the appearance of 'polycystic-appearing' ovaries, either on laparoscopy or sonography, is not exclusive or diagnostic for PCOS, rather it is a sign of inadequate and/or arrested folliculogenesis [16]. Between 21 and 23% of unselected women appear to demonstrate this ovarium appearance [17–19]. Although the majority of patients with 'polycystic ovaries' detected ultrasonographically demonstrate either oligomenorrhea, hirsutism, or both, up to 25% of patients with this sonographic picture may be entirely asymptomatic [20]. Furthermore, up to 40% of patients with 21-OH deficient NCAH also demonstrate polycystic ovaries ultrasonographically [21]. Finally, it is clear that not all patients with FAE demonstrate polycystic ovaries [17,20,22–24], and even with more sophisticated computerized measurements of ovarian stroma overlap between normals and patients with FAE is significant [25]. Overall, sonographic or his-

topathologic evidence of polycystic ovaries should be considered only one of the many signs of FAE. Few of the above studies have included biochemical or hormonal data on the probands and/or family members. Hence, a narrow inclusion criteria yields an incomplete, and potentially biased, view of the inheritance of this disorder.

2. *Incomplete characterization of the phenotype in family members:* Characterization of the phenotype of FAE (or PCOS) in family members has generally been incomplete, with most investigators using only clinical examination and/or ovarian ultrasonography. Only one report [14] studied family members biochemically. The majority of the studies currently available present either indirect or incomplete data on probands and/or relatives, often neither reporting nor confirming the physical, biochemical or historical characteristics. In fact, the least reliable method of gathering family data, interview of only the proband, was used in two of the above clinical studies [11,13]. Another study only used interviews of the relatives, without physical examination [10]; and in yet another, only facial examinations of family members was used [9].
3. *Non-inclusion of male relatives:* Previous investigations have focused on the heritability of female relatives of patients with FAE. Nonetheless, even though FAE, by definition, exclusively affects women, male family members should be included in studies of genetic inheritance. As such, even if the disorder is presumed to be clinically evident only in females, it is probable that males are carriers of relevant molecular genetic abnormalities. Thus, inclusion of males in family studies evaluating molecular markers is essential to develop an accurate inheritance model. Secondly, while it is presumed that FAE and its associated metabolic abnormalities are not clinically evident in men, this may not be the case at all. Perhaps these males also demonstrate a higher incidence of metabolic abnormalities, such as insulin resistance, lipid abnormalities, and cardiovascular disease. As noted above, it appears that affected males may suffer from a greater incidence of PMPB [14]. However, testing the hypothesis that a male FAE phenotype exists is not possible without the study of male relatives. Finally, the inclusion of males in these studies may increase the accuracy of the segregation ratios obtained, particularly if a male marker(s) for FAE affection is established.
4. *Possible inclusion of patients with non-classic adrenal hyperplasia:* Between 1% and 10% of women with androgen excess suffer from 21-OH deficient NCAH, depending on ethnicity [21]. Unfortunately, most investigators did not clearly exclude this disorder in their studies—which while others purposely included patients with CAH [12]. Inclusion of these families may confound linkage analysis and the calculation of segregation ratios.
5. *Lack of appropriate control data:* In some of the studies controls were not included [10,12,14], preventing an adequate determination of whether the prevalence of FAE/PCOS among female relatives was significantly different than expected. While the inclusion of 'control families' is not necessary, at a minimum the prevalence of the disorder in the general population being studied should be first determined for comparison.
6. *Restrictive ethnic/racial focus:* Clinical, and particularly molecular (see below) genetic investigations of any disorder are best conducted in racially/ethnically homogeneous study populations, in order to minimize the effect of the confounding variables. Nonetheless, it then becomes difficult to extrapolate the finding from one ethnic/racial/geographic population to others. For example, in the study of the genetics of androgen excess, little to no data is available from Black populations. Investigators generally either study predominantly white Caucasian individuals, or do not describe the racial mix of the population studied. Furthermore, with two exceptions [8,9], the majority of studies determine the heritability of the disorder in Europe. The importance of studying distinct ethnic and/or geographic groups, in order to determine any difference in prevalences or heritability, is strongly emphasized.

As newer studies are designed and performed these critiques need to be considered and corrected to the extent possible. In our own investigations we have addressed most, although not all, of these issues.

2. Current data

The immediate objectives of our investigations (see below) included determining the degree of heritability, the mode of inheritance, and the rate of paternal/maternal inheritance; and estimating the risk of an individual for having FAE/PCOS, based on family history. Additionally, our laboratory has been involved in the elucidation and testing of various candidate genes, although a discussion of these is beyond the scope of the present review. Firstly, in an attempt to obtain a rough estimate of familial tendency, we initially surveyed 250 consecutive unselected and untreated patients with PCOS (i.e., probands) who presented for care at the University of Alabama at Birmingham. The racial composition of the study group was 86% Caucasian, 13% Black and 1% other. Of these 250 probands, 188 (75%) reported having at least one other female relative with hirsutism and/or oligome-

Table 2
Prevalence of self-reported features of PCOS among 1452 living female relatives of 250 consecutive PCOS probands[a]

	Total No.	Hirsutism and/or oligomenorrhea	Hirsutism and oligomenorrhea
Mothers	224	118 (53%)	42 (19%)
Sisters	238	113 (47%)	40 (17%)
Maternal aunts	418	99 (24%)	15 (4%)
Paternal aunts	352	92 (26%)	17 (5%)
Maternal grandmothers	115	24 (21%)	4 (3%)
Paternal grandmothers	105	24 (23%)	3 (3%)

[a] By interview of proband and/or relative only.

norrhea. Based on proband and family member interviews, our data indicated that approximately 50% of mothers and sisters, one-quarter of maternal and paternal aunts, and 20% of maternal and paternal grandmothers had hirsutism and/or oligomenorrhea (Table 2). These data were highly suggestive of an autosomal dominant mode of inheritance. However, if solely the combination of hirsutism and oligomenorrhea (suggestive of PCOS) was considered, only 20% of mothers and sisters, and 5% or less of second degree family members were affected. This final observation was neither suggestive of autosomal dominant nor autosomal recessive inheritance, again stressing the importance of considering hirsute hyperandrogenemic women as part of the PCOS continuum.

Secondly, the mothers and sisters of 97 PCOS patients were recruited to undergo a full clinical and hormonal evaluation in order to confirm the observations noted in the interviews. Family members were deemed affected if they had evidence of PCOS, i.e. a history of oligomenorrhea, in conjunction with hirsutism (a modified Ferriman–Gallwey score ≥ 6) and/or hyperandrogenemia (i.e., elevated levels of total or free testosterone, and/or androstenedione). Individuals who were postmenopausal and/or on hormonal therapy were deemed affected if they had a history of oligomenorrhea and hirsutism. Nonetheless, incomplete evaluation of postmenopausal or hormonally treated family members may decrease the ability to detect PCOS and raises a potential bias. Nineteen out of 44 (40%) sisters and 15 out of 83 (18%) mothers studied fit these diagnostic criteria for PCOS. Furthermore, of those family members who were not considered to be PCOS, an additional 14% of mothers and 8% of sisters had either isolated hirsutism or oligomenorrhea. Some of these family members may actually have a mild form of PCOS, consistent with variable expressivity of the disorder. The segregation ratio for PCOS among sisters was 0.40, suggestive that disorder appears to be caused by a dominant gene effect. Nonetheless, the prevalence of PCOS in the mothers was less than expected (i.e., 0.50) if the inheritance were dominant and the rate of maternal and paternal inheritance was equal. The lower segregation ratio for mothers may be due to decreased fertility in affected women and/or the incomplete evaluation of postmenopausal mothers.

Thirdly, and in order to confirm that the maternal and paternal inheritance of FAE/PCOS was equal, we studied 23 families in which 75% or more of living female relatives were able to be interviewed. Of these eight (35%), eight (35%) and seven (30%) demonstrated a maternal-only, a paternal-only, or a combined maternal/paternal inheritance pattern, respectively. These data support the concept that FAE/PCOS is equally inherited from the mother's and the father's side. Hence the lower affection rate among mothers (19%) compared to sisters (40%), or that predicted for an autosomal dominant disorder (50%) is due either to reduction in fecundability of affected mothers, or to nondetectability of the disorder in menopausal and/or hormonally treated individuals.

3. Conclusions

A number of obstacles to the completion of accurate family studies of FAE/PCOS have been identified. Importantly, the clinical heterogeneity of the disorder has been a significant confounding factor. Diagnostic criteria and phenotypes to be considered should be selected so as to include the entire range of the disorder, minimizing the number of affected individuals who are not 'detected'. For example, individuals with significant hirsutism and elevated serum androgens, in conjunction with apparently normal ovulation (at the time of evaluation), are generally not diagnosed with PCOS and are not included in genetic studies. Another potential cause of nondetectability includes difficulties with the collection of critical clinical and biochemical data. For example, women who are postmenopausal and/or on hormonal therapy cannot be evaluated for biochemical abnormalities. Unfortunately, affected individuals are also those at increased risk of receiving hormonal therapy and/or surgical castration. Furthermore, recall of menstrual cyclicity in these women might not be accurate. It should be noted that, a recall of 'regular cycles' is not proof of regular ovulation among hirsute women, as approximately 40% of

these actually demonstrate oligo/anovulation when their ovulatory function is monitored more closely [6].

Hirsutism, a major diagnostic criterion, is also affected by many factors which can make evaluation difficult. Both extensive electrolysis, shaving the morning of clinical examination, and prior hormonal therapy can decrease the severity of clinically evident hirsutism. Furthermore, the impact of age on the degree of hirsutism needs to be considered. For example, while hirsutism progresses with age, patients are also observed to improve clinically as they near menopause and thereafter. Finally, as a phenotype for 'carrier' males has not been clearly established, linkage studies may be limited by the small numbers of individuals within an affected family.

As has been previously reviewed [25] there are three potential probable modes of inheritance. The first inheritance model considers FAE/PCOS to be a single-gene disorder, either recessive or dominant, and following the Mendelian form of inheritance. With this 'single-gene Mendelian' model, one would expect to find the prevalence of PCOS to be 50% among first degree relatives, and 25% among second degree relatives. Furthermore, if the disorder were caused by the action of one single genetic defect, with minimal environmental and/or other genetic influences, the phenotypes within a single affected family might be expected to be very similar. However, our preliminary data suggests that the segregation ratio among sisters is <0.50, and we have observed a significant degree of phenotypic heterogeneity within affected families, not supporting this inheritance model for FAE/PCOS.

The second model defines the FAE/PCOS as 'multifactorial', and suggests that this disorder simply represents the conglomeration of abnormalities already present separately and, to a significant degree, in the general population. Under this concept, PCOS would be considered to be a multifactorial disorder with some genetic influences, such as NIDDM and CVD. As such, many unaffected women (and men) in the general population could demonstrate PCOS-related defects in an isolated manner. However, women carrying multiple defects (both via inheritance and via environmental influences) would be at increasing risk for developing clinical PCOS. Our data do not contradict this model, although the higher heritability rate and early disease onset make it unlikely that FAE/PCOS is another such complex multifactorial disorder.

Our data primarily supports a third mode of inheritance, which we term the 'variable expression-single gene' model. This model includes features from the first two proposed modes of inheritance. Under this concept, PCOS is caused by a single major gene defect, which is transmitted to 50% of offspring. However, the expression of PCOS would then be modified by additional factors, both environmental and/or genetic (i.e., 'genetic background'), such that the actual observed segregation ratio could be less than expected for an autosomal dominant disorder (i.e., 0.50). Theoretically, women who possess the mutation would be at almost 100% risk of developing some degree of PCOS, although additional factors would determine the clinical severity of the disorder. Genetically predisposed women not exposed to these other influences may develop only subclinical forms of PCOS or present with isolated diagnostic features also seen in PCOS (e.g. hyperandrogenemia-only) but not the full disorder.

In conclusion, our preliminary data suggests that PCOS is a familial disorder, with a single autosomal dominant gene effect, that presents with a variable phenotype. Inheritance appears to be equally probable from the maternal as from the paternal side of the family, although expanded clinical studies which include both maternal and paternal aunts will be required to confirm these findings. Nonetheless, our clinical data suggests that the affection rate among mothers is less than expected, which may be due to decreased fertility of affected mothers, or to our inability to detect the disorder in older, menopausal or hormonally treated individuals. Finally, it appears that a woman's risk for developing PCOS is approximately 40% if her sister is affected. In accordance with the rules of dominant inheritance it might also be surmised that the risk would be similar if a woman's mother were affected, although this risk remains to be determined in prospective studies. Considering FAE/PCOS to be a dominant genetic disorder with a high degree of expressivity, we propose that the risk for developing FAE/PCOS is determined by family history. However, the highly variable phenotype of PCOS further suggests that, besides a single genetic mutation, other factors must be contributing to the development of the disorder. These factors may include environmental influences, such as fat and carbohydrate consumption, exercise level, peripubertal stress and/or hormonal exposure; and additional genetic defects, such as those that regulate insulin secretion or determine body type.

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