

Evolutionary determinants of polycystic ovary syndrome: part 1

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Polycystic ovary syndrome (PCOS) is a common and complex genetic disorder that develops under varying degrees of hyperandrogenemic and hyperinsulinemic conditions that cause phenotypic variability ranging from mild hirsutism to anovulation and infertility. In addition to increased risk of reproductive disability, PCOS is associated with metabolic diseases including type 2 diabetes, dyslipidemia, and cardiovascular disease. Similar prevalence rates and shared genetic susceptibility of PCOS among different populations suggest that genetic risk factors were already present in the ancestors of humans. Contemporary human genetic studies inform us that the origin of human ancestors is from Africa. Sharing common susceptibility loci between Chinese and European ancestry suggests that PCOS may have persisted for more than 50,000 years, before the migration of humans out of Africa. Although PCOS is the most common cause of anovulatory infertility, its high prevalence is still a paradox. From an evolutionary perspective, the pathogenic mechanisms underlying PCOS might be candidate factors for survival advantage of the human being. Former compensatory advantageous factors may become pathogenic mechanisms underlying complex metabolic disease with prolonged life expectancy and transition to sedentary lifestyle. (Fertil Steril® 2016;106:33–41. ©2016 by American Society for Reproductive Medicine.)

Key Words: Polycystic ovary syndrome, genetic, evolution, genome-wide association study, human development, Göbekli Tepe

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P COS is a complex genetic disorder of women in reproductive age (1). The prevalence of PCOS according to proposed diagnostic criteria has been reported to be 6%–19% in different studies (2, 3). The syndrome is characterized by hyperandrogenism, chronic oligo-/anovulation, and insulin resistance, and it is associated with increased risk of reproductive disability and metabolic diseases such as type 2 diabetes, dyslipidemia, cardiovascular disease (4, 5). The interactions of multiple inherited genetic factors related to hyperandrogenism and environmental or acquired factors, such as sedentary lifestyle and westernized dietary habits, can together trigger the dysregulation of androgen synthesis, which is the main factor causing ovarian follicles not to grow as much

as a dominant follicle, resulting in oligo-/anovulation. The secretion dynamics of GnRH pulses are changed due to lack of progesterone peaks through the luteal phase of the menstrual cycle, which in turn leads to the increase of LH secretion. An increased LH secretion causes stimulation of androgen synthesis and secretion by the ovaries. The adrenals also contribute to androgen excess in PCOS (6). The inherited genetic factors and westernized lifestyle can also induce insulin resistance and/or obesity that both cause a hyperinsulinemic milieu and low-grade chronic inflammation, which are other stimulators of androgen synthesis (1). Consequently, PCOS develops under varying degrees of hyperandrogenemic and hyperinsulinemic conditions that cause phenotypic

variability ranging from mild hirsutism to anovulation and infertility.

In simple terms, an evolutionary approach aims to understand the life history of an organism or a phenotypic trait. To be classified as a subject of an evolutionary study, first the phenotypic trait of interest should demonstrate variation in the population under study. Second, some proportion of the variation should be genetic; therefore, the trait should be heritable. Finally, the phenotypic trait should have an effect on fitness. PCOS, as a phenotypic trait, clearly fulfills all of these three requirements, and as a clinically important phenotype transcending human evolution it is a good case for evolutionary medicine (7).

When traditional proximate (immediate) cause-oriented medicine is not sufficient to fully understand a disease and offer innovative therapies, a novel approach focusing on the ultimate (evolutionary) causes underlying a chronic condition such as PCOS has a lot to offer to medicine (8). Ultimate causes affect human populations for much longer spans of time, on the order

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of thousands of generations, compared with the short life span of an individual. An evolutionary approach to the life history of PCOS can give us an important perspective for understanding the adaptive value of traits underlying the disease, with certain traits, such as hyperandrogenism and insulin resistance, being advantageous at one stage of human development (prehistoric times) and detrimental at another stage (modern times). In this succinct review on the evolutionary determinants of PCOS, we start with a synopsis of human development, followed by a determination of how long PCOS has been with the human lineage based on evidence from genetic data. Finally, we discuss possible selective advantages that the major PCOS clinical traits might have conveyed in our ancestors.

A SYNOPSIS OF HUMAN DEVELOPMENT

Similar prevalence rates of PCOS among different contemporary human populations (2, 9, 10) and shared genetic susceptibility among these different groups (11) suggest that the genetic risk factors were already present in our human ancestors before they migrated out of Africa. This suggestion necessitates a closer look at the history of human development.

Anthropologic and molecular studies show that humans diverged from their most common recent ancestors with chimpanzees around 6 million years ago and evolved in Africa adapting to the ever-changing needs in their environment (12, 13). Comparative morphology and paleontologic studies reveal that physiology, body shape, brain size and associated tool-making and communication skills, diet, and social structure were changing, in what appears to be in burst intervals, since the early hominids to anatomically modern humans (14–18). Up until 50,000 years ago, Africans with more modern skeletons were lean-bodied simple hunters directed at easy-to-kill land animals. These are the conditions that most probably selected the metabolic thrift, increased fat storage, and muscle and bone strength in our early ancestors.

By the Late Stone Age, around 50,000 years ago, coinciding with the major dispersal of humans out of Africa, sometimes called the Great Leap Forward, more sophisticated stone tools and cultural artifacts began to appear and hunter-gatherer societies started to exhibit accelerating cultural evolution and larger and denser populations (19). Late Paleolithic (40,000–10,000 years ago) people were rather inventive and made technologic innovations that enabled them to inhabit new niches, including rather cold and harsh geographic areas (20). The vital statistics of Late Paleolithic people are rather hard to decipher owing to scarcity of remains. It is argued that child mortality was high, women died before the age of 40 years (possibly owing to risks associated with childbearing) and men before the age of 60 years. Their community groups contained more older people, possibly enhancing group survival, and enabling young women to have additional children much sooner, explaining the larger and denser populations (21). In this new social structure, “grandmothering” might have been an advantage selected for that allowed for the longer post-reproductive life span unique to humans.

Hunter-gatherer groups became increasingly more adapted to sedentary lifestyles, better managing their proximate natural resources, which led to an agricultural revolution in the Near

East (Fertile Crescent), China, and Mesoamerica around 10,000 years ago, initiating the cultural period of the Neolithic (22–24). The sudden population increase could, in part, be due to better nutrition, which fostered the development of earlier menarche in women, resulting in a longer period of fertility, and a stable food supply might mean fewer miscarriages and childhood deaths. Also, decreased mobility allowed for shorter intervals between births.

However, the development of agriculture and animal domestication also imposed a heavy disease burden on practicing societies, in some cases reducing the average life expectancy to lower levels than those of hunter-gatherers (23, 25). Dependence on fewer crops might have led to selective nutrient deficiencies. And animal-derived and -transmitted infectious diseases (zoonosis) and the development of epidemics owing to the high population density exerted a significant selection on these populations, signatures of which are still evident in our genetic makeup today. Therefore, early reproduction age success should still have been rather important in these communities.

HOW LONG HAS PCOS AFFECTED HUMANS? EVIDENCE FROM GENETIC DATA

In line with the fossil record hypothesis that modern humans arose in Africa around 200,000 years ago, human genetic studies demonstrate that all modern human mitochondria and Y chromosomes are descendants of their respective common ancestors in Africa (26–28). Today, most human genetic diversity is found in Africa, and the vast majority of genetic diversity is found within populations rather than between human populations (29–31). Humans are genetically a very homogeneous species, where the average difference between two human genomes is less than 0.1% (32, 33) indicating a very small effective population size (the number of individuals in a population who contribute to the offspring to the next generation) (34, 35).

One of the methods to understand human evolution is to estimate the history of human population size (36). Individual genome-sequencing studies are also potentially informative regarding human evolution (37). The Khoisan-speaking hunter-gatherer populations of southern Africa, also called collectively the San, and other native groups from central and southern Africa, exhibit the highest known levels of genetic divergence from other populations. Therefore this important genetic feature was used in a study aimed at investigating ancient human demography, and the San’s divergence time was estimated to be around 130,000 years ago (38). The study also predicted that ancestors to Chinese and Europeans diverged from Africans about 50,000 years ago.

Taken together, contemporary human genetic studies inform us that since their origin from an African common ancestor, humans have been through multiple evolutionary bottlenecks, particularly affecting those populations moving out of Africa, resulting in only a small number of individuals contributing to today’s genetic pool diversity (37, 38).

With the advance of very-high-throughput genotyping technologies, we began to understand the influence on PCOS of this small, but significant, genome-wide variation observed between and among human populations. The first

genome-wide association study (GWAS) on PCOS was conducted in Chinese women and identified three susceptibility loci (2p16.3, 2p21, and 9q33.1, related to the genes *LHCGR*, *THADA*, and *DENND1A*) (39). In a subsequent study, in addition to those three loci, eight new susceptibility loci (9q22.32, 11q22.1, 12q13.2, 12q14.3, 16q12.1, 19p13.3, 20q13.2, and a second independent signal at 2p16.3) were identified in a new Chinese ancestry cohort (40). It was found that single-nucleotide polymorphisms (SNPs) in several candidate genes (*C9orf3*, *FSHR*, *INSR*, and *HMGA2*, *YAP1*, *RAB5B/SUOX*, *TOX3*, and *SUMO1P1*) were related to hormones and organ growth, respectively. Similar genetic alterations were also identified in type 2 diabetes (41, 42).

The effects of these loci on PCOS have been replicated in women of European ancestry (43–46). A meta-analysis evaluating cross-ethnic effects of these Chinese PCOS loci in northern European ancestry demonstrated that 12 out of 17 genetic variants mapping to these loci had similar effect size and identical direction, representing a common genetic susceptibility profile for PCOS across different ethnic groups (11). Recently, seven Chinese PCOS loci were replicated in a Korean GWAS (47). The latter study also identified new susceptibility loci for PCOS, and the strongest association was observed in an SNP at chr 8q24.2, located upstream of the *KHDRBS3* gene, which is associated with telomerase activity and may trigger the PCOS phenotypes. All of the aforementioned studies used the Rotterdam 2003 criteria as the diagnostic tool for PCOS, which allows for the detection of multiple PCOS phenotypes (48).

The phenotype of PCOS at greatest risk for insulin resistance and its related metabolic features are those defined by the National Institutes of Health (NIH) 1990 criteria (49, 50). More recently, common genetic susceptibility loci in a GWAS were mapped in European-ancestry women who fit the phenotype of PCOS described by NIH (51). In addition to the locus chr 9q22.32, which was previously reported in the Chinese PCOS cohort, two novel loci, chr 8p32.1 and chr 11p14.1, were identified in this study. Chr 11p14.1 was in the region of the FSH β -polypeptide (*FSHB*) gene, and the chr 11p14.1 SNP, rs11031006, was strongly associated with both LH levels and the PCOS phenotypes of NIH.

Shared common susceptibility loci between Chinese and European ancestry suggests that these loci could be conserved genetic susceptibility factors for PCOS. When we consider the time that it took for Chinese and Europeans to migrate from Africa and then racially diverge, PCOS may have persisted for more than 50,000 years (51, 52). In addition, the similar prevalence rates of PCOS between different nations, when using same diagnostic criteria (2, 9, 10), supports this assumption (52). Finally, studies evaluating the effect of excess calorie intake and obesity demonstrate surprisingly limited effects of these burdens on the prevalence of PCOS, particularly in populations with very high background prevalence rates of overweight and obesity (53, 54).

WHY PCOS?

Although PCOS is the most common cause of anovulatory infertility all over the world, its high prevalence is still a great

enigma and paradox. From an evolutionary perspective, the increasing prevalence of complex metabolic disorders such as obesity, diabetes, and PCOS in developed and developing countries brings attention to the idea that genetic triggers leading to pathogenic mechanisms underlying these syndromes might be candidate factors for survival advantage of the human being (55–58). Former compensatory and advantageous factors may become pathogenic mechanisms with prolonged life expectancy and transition to sedentary lifestyle, underlying the development of complex metabolic diseases (59).

Hyperandrogenemia as a Positive Selective Force

One of the most common autosomal recessive genetic disorders is nonclassic congenital adrenal hyperplasia (NCAH), largely caused by mutations in *CYP21A*, which encodes for the enzyme cytochrome P450c17, determining 21-hydroxylase activity (60). Carrier frequency of these mutations is nearly 10% in all populations. It was proposed that these mutations might have compensatory advantages like those seen in heterozygous individuals with sickle cell hemoglobinopathy, who are resistant to malaria infestation (55). According to this hypothesis, early puberty and masculinization caused by increased adrenal androgen secretion due to NCAH might constitute a selective force for women and their children in the setting of struggle and recurrent cruelty. Similarly, the increased bone mineral density (61–65), muscle mass, and strength (64–67) observed in women with PCOS may provide a positive selective evolutionary force.

Another hypothesis is that the protective role of adrenal DHEA on the immune system can be a positive genetic selective force to respond to endemic diseases (55). In addition to adrenal androgen hypersecretion, Witchel et al. (56) demonstrated brisk cortisol response in *CYP21A* heterozygote carriers of 21-hydroxylase deficiency and postulated that this response might be protective against inappropriate immune responses and facilitate the restoration of homeostasis in response to infectious, inflammatory, or other stressor factors.

Role of Insulin Resistance

Insulin receptor (*INSR*) has a central role in insulin metabolism and mutations in *INSR* can cause severe hyperinsulinemia and insulin resistance (68–70). According to a recent GWAS (40) and other earlier studies (71, 72) on PCOS, one of the evolutionary inherited susceptibility loci is associated with *INSR*. Insulin resistance is evolutionarily well preserved in insects, worms, and vertebrates, including humans, meaning that it provides a compensatory advantage for survival (73). Why has insulin resistance persisted through the evolution of modern humans? Evolutionary approaches to metabolic diseases hypothesized that our ancestors left us vulnerable to diseases because of inheritance of a thrifty gene that organizes the insulin action/resistance according to the phases of feast and famine (seasonality and uncertainty of the food supply) of the hunter-gatherer lifestyle (74). The most important role of insulin resistance during prolonged starvation is to minimize protein losses by diminishing the necessity to utilize amino acid carbon skeletons to produce glucose, which is

the major determinant of long-term survival in starving individuals (75). It was recently hypothesized that insulin resistance (or a capacity of selectively modifying the cellular/tissue response to insulin) provides glucose availability for inflammatory responses to protect from starvation, disease, and trauma, as well as to promote growth during pregnancy, puberty, and cancer, and in preparing the organism for migration/hibernation (76).

A different perspective on the development of hunter-gatherer communities was offered by the 1963 discovery of Göbekli Tepe, in the southeastern part of Turkey, one of the oldest religious sites identified to date (77). German archaeologist Klaus Schmidt (78) suggested that Göbekli Tepe was built by hunter-gatherer humans during the early Neolithic (New Stone Age) period, having developed rapidly to form a large-scale social organization rather than through the recognized process involving increasing sedentary community as small-scale farming developed (79). In this setting it is possible that hunter-gatherers might have also had to deal with infectious and ecologic diseases, as well as social problems in a setting of struggle, as one of the causes of death before the Neolithic revolution. According to Schmidt's suggestion (79), high levels of social stressors might have been the main selection factors for hyperandrogenemia and insulin resistance to protect organisms against stress and prolonged starvation.

When the human lifestyle changed from hunter-gatherer to sedentary-agricultural, and acquiring food was now less of a limitation, the defensive mechanisms selected for, including insulin resistance, might now act against the organism. Although insulin resistance protects the organism from starvation and social stress, in the setting of food abundance it favors the development of metabolic disorders such as PCOS (59).

Role of the Changed Dynamics of Gonadotropins

A dysregulation of androgen synthesis is another major pathogenic factor for PCOS. Genomic variants related to hyperandrogenism may contribute to this dysregulation. Variants in *FSHR* (FSH receptor) have been considered as a candidate gene for PCOS (80). Recent GWAS reports on PCOS revealed that one of the inherited susceptibility loci was near *FSHR* (40). Another possible evolutionarily inherited susceptibility locus for PCOS demonstrated by a recent GWAS in European-ancestry women with NIH PCOS phenotype is near *FSHB/ARL14EP* (51). The SNP in this locus was strongly associated with both LH levels and PCOS diagnosis. The GWAS (51) also demonstrated that LH mediated the association with *FSHB*, and that variation in *FSHB* contributes to major changes in secretion of gonadotropin in PCOS. Another locus demonstrated by the same study (51) was in the region of *GATA4*, implicated in regulation of gonadal development and steroidogenic genes. Deletion of this gene disrupts the gonadotropin responsiveness (81). Another GWAS in PCOS (82) uncovered a new susceptibility allele near *FSHB* which was strongly associated with higher LH/FSH ratios, possibly promoting ovarian androgen production and follicular growth arrest (83).

Although FSH regulates ovarian folliculogenesis, which is dysfunctional in PCOS, LH regulates theca cell testosterone synthesis, which is increased in PCOS in an LH-dependent

manner (84). Variants at the loci related to gonadotropin actions (*LHCGR* and *FSHR*) might have contributed to ovarian follicles not growing as much as a dominant follicle, i.e., through defective FSH action. Similarly, variants at the loci related to gonadotropin secretion (*FSHB*) might have led to hyperandrogenemia, i.e., through increasing LH levels (leading to increased androgen synthesis and secretion by the ovaries and adrenals, which negatively affects ovarian follicle growth as well).

From the evolutionary perspective, changes in gonadotropin dynamics, like those seen in the PCOS phenotype, might have been among the compensatory adaptation mechanisms leading to decreased ovulation and conception. Considering the aforementioned adaptive evolutionary changes one can speculate that early human lineages lived in small hunter-gatherer communities, had to efficiently utilize food energy, and had few children to care for. In a population-based study, women suffering from oligo-amenorrhea and/or hirsutism (major phenotypic features of PCOS) were compared with non-symptomatic women (85). Having both oligo-amenorrhea and hirsutism was found to be associated with the least fecundability rate. These symptomatic women also had a smaller family size than nonsymptomatic women. Another recent study reported that women with PCOS had lower pregnancy experiences per woman than healthy women (86). Natufian women, in an Epipaleolithic culture that existed from 12,500 to 9,500 BC in the Levant and lived as semisedentary hunter-gatherers, gave birth less frequently and lived longer than men, who had to perform higher hunting activities and deal with social conflicts (87). Decreased fecundability and number of pregnancies, as a result, decreased the family size of women with PCOS, which in turn might have favored maternal and infant survival during prehistoric times (56, 58, 59). Maternal mortality may have been reduced in ancient PCOS women. Therefore, PCOS might also have led to a rearing advantage by providing more child care and food compared with women without PCOS.

By the Neolithic revolution, in which farming started, improved food resources might have favored human health and consequently life expectancy and fertility. Having a bigger family was an advantage to provide more labor force for agricultural communities. However, Neolithic transition affected men and women differently, and men experienced a longer life expectancy than women (87). Because of the earlier onset of pregnancy and increase in number of births, adult female mortality might have increased. Lower pregnancy rate than women without PCOS might have protected Neolithic PCOS women from an increased maternal mortality. Nevertheless, with initiation of coitus ability at early age, occurrence of coital habitus more frequently, and the absence of common obesity together with relative insulin resistance, which may have served more energy to women, ancient PCOS women may have experienced more pregnancy than at present (52).

Leptin and Adipose Tissue Expandability Hypothesis

Lipodystrophies characterized by leptin insufficiency or deficiency are associated with PCOS phenotype and insulin

resistance (88–90). Furthermore, the effect of leptin replacement on LH secretion and restoration of menstrual cycles has already been demonstrated in patients with lipodystrophy (91). In addition to the role of leptin in fertility (92), its importance in pregnancy, fetal development, and pubertal growth has been shown in novel studies (93, 94).

Evolution along the human lineage also produced rather unique life history patterns, such as extended gestation time, longer juvenile period, delayed maturation, and longer life span (95–99). An extended gestation time and a longer juvenile period could be directly related to seasonality and deficiency of the food supply, which could lead to an insufficiency of fat tissue and its hormones, such as leptin. Accordingly, seasonal changes in food supply seen in the hunter-gatherer lifestyle might have contributed to PCOS phenotype by means of seasonal variation in leptin levels as a compensatory adaptation. Although seasonal leptin deficiency leading to insulin resistance may have minimized protein losses, it might also have interfered with the dynamics of gonadotropins to prevent ovulation and conception during prolonged starvation.

According to the adipose tissue expandability hypothesis, which explains the insulin resistance in both obesity and lipodystrophy, subcutaneous adipose tissue has a restricted capacity, and various environmental and genetic factors can define the limits of an individual's subcutaneous lipid storage (100). When these limits are exceeded, lipotoxicity, character-

ized by low-grade inflammation and insulin resistance, emerges and subsequently hyperandrogenemia can develop. The dramatic and rapid changes of human behaviors may have led to the overfilling of subcutaneous fat depots, especially in people who carried a susceptibility allele for PCOS.

Impact of Rapid Changes in Lifestyle

The hunting-gathering lifestyle evolved to sedentary life about 350 generations ago with the agricultural revolution. The industrial revolution brought more sedentary life experiences for humans about seven generations ago (101–103). Within the past two generations, beyond the sedentary life, an “almost immobile” lifestyle has emerged under the effect of the digital revolution. The lifestyle of recent generations would be the exact opposite of the definition of hunter-gatherer lifestyle. In parallel to the large decrease in the need of physical activity, average food intake also dramatically increased compared with the preindustrial agrarian societies in which obesity and amount of consumed food were very low, and average calorie intake was less than 2000–2500 kcal/day until the eighteenth century (58). Therefore, the dramatic and rapid changes of human behaviors may not have permitted any compensatory adaptations. The proposed protective PCOS phenotype, even for the Neolithic period, could have turned into a diseased phenotype, especially in those who carry the susceptibility genes for PCOS.

TABLE 1

Allelic nature and population frequency distribution of genetic variants associated with polycystic ovary syndrome (PCOS) in multiple GWAS.

Gene	SNP	Allelic nature ^a			Effect on PCOS	Effect allele population frequency ^b				
		Ancestral	Derived	PCOS ^c		African	European	East Asian	South Asian	American
<i>FSHR</i>	rs2268361	C	T	C	Protective	0.75	0.36	0.50	0.46	0.37
<i>C9orf3</i>	rs4385527	G	A	G	Protective	0.90	0.60	0.18	0.77	0.65
	rs3802457	G	A	G	Protective	0.72	0.98	0.89	0.97	0.97
<i>DENND1A</i>	rs10993397	C	T	C	Protective	0.87	0.60	0.73	0.71	0.65
	rs10986105	T	G	T	Susceptible	0.15	0.04	0.05	0.06	0.08
<i>SUMO1P1</i>	rs6022786	A	G	A	Susceptible	0.57	0.41	0.41	0.44	0.34
<i>GATA4/NEIL2</i>	rs804279	A	T	A	Protective	0.64	0.73	0.81	0.74	0.78
<i>KRR1</i>	rs1275468	C	T	C	Susceptible	0.62	0.70	0.57	0.68	0.66
<i>ERBB3</i>	rs7312770	C	T	C	Susceptible	0.51	0.46	0.22	0.31	0.31
<i>THADA</i>	rs12468394	A	C	C	Protective	0.54	0.48	0.73	0.34	0.70
	rs12478601	T	C	C	Protective	0.18	0.41	0.71	0.34	0.60
<i>LHCGR</i>	rs7563201	G	A	A	Protective	0.37	0.53	0.28	0.55	0.31
	rs13405728	A	G	G	Protective	0.32	0.07	0.27	0.17	0.19
<i>DENND1A</i>	rs10818854	G	A	A	Susceptible	0.08	0.05	0.05	0.08	0.07
	rs10760321	G	A	A	Susceptible	0.65	0.71	0.65	0.66	0.73
<i>YAP1</i>	rs1894116	A	G	G	Susceptible	0.07	0.08	0.18	0.22	0.05
	rs11225154	A	G	A	Susceptible	0.02	0.08	0.19	0.24	0.05
<i>RAB5B/SUOX</i>	rs705702	A	G	G	Susceptible	0.05	0.32	0.22	0.20	0.23
<i>HMGA2</i>	rs2272046	A	C	C	Protective	0.001	0.03	0.08	0.03	0.01
<i>TOX3</i>	rs4784165	T	G	G	Susceptible	0.44	0.26	0.36	0.27	0.33
<i>INSR</i>	rs2059807	G	A	G	Susceptible	0.82	0.62	0.37	0.68	0.47
<i>KHDRBS3</i>	rs10505648	A	G	G	Protective	0.28	0.52	0.09	0.27	0.36
<i>KCNA4/FSHB</i>	rs11031006	G	A	A	Susceptible	0.05	0.15	0.03	0.10	0.10
<i>ERB4</i>	rs1351592	C	G	G	Susceptible	0.64	0.19	0.09	0.28	0.21
<i>RAD50</i>	rs13164856	C	T	T	Susceptible	0.63	0.70	0.62	0.69	0.58
<i>ERBB2</i>	rs7218361	G	A	A	Susceptible	0.002	0.05	0.0	0.02	0.03

^a Information based on dbSNP and 1000 Genomes data.

^b Allele state associated with PCOS.

^c Frequency of PCOS-associated alleles among human population samples in 1000 Genomes project.

Ünlütürk. Evolutionary determinants of PCOS. Fertil Steril 2016.

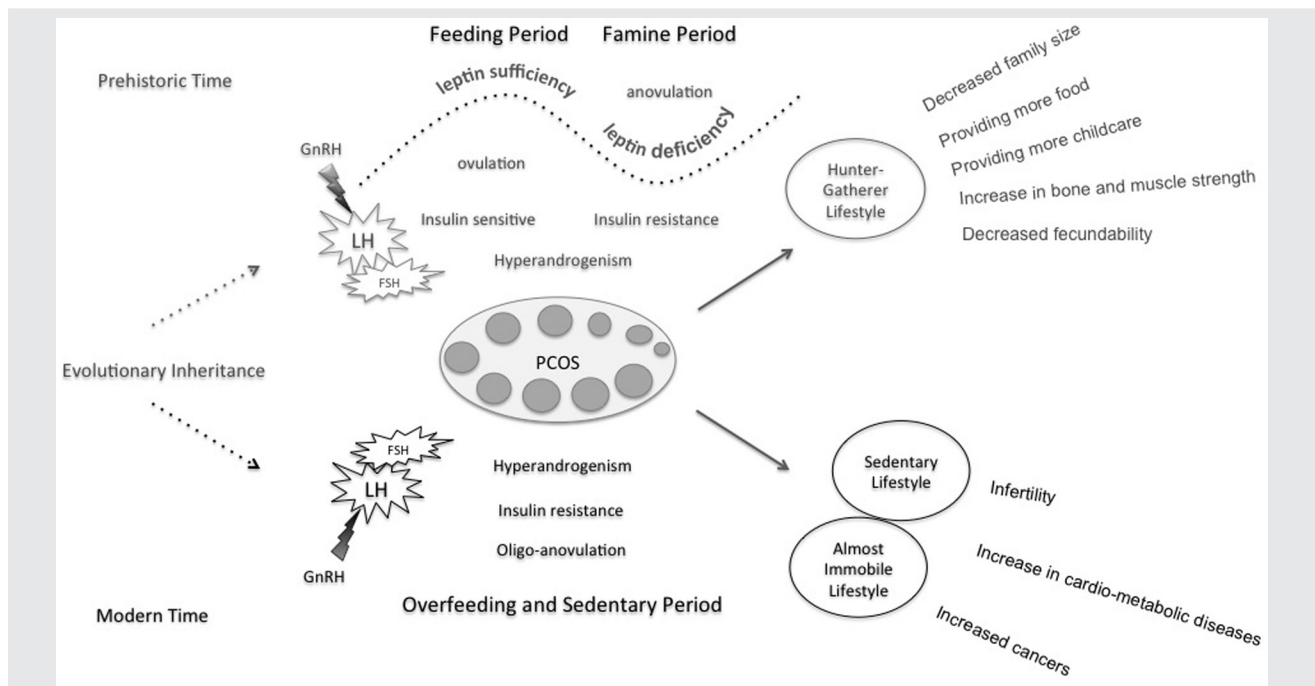
With the obesity epidemic of recent decades, studies have suggested that excess weight may be increasing the prevalence of PCOS (3, 104, 105) and may be unmasking previously latent PCOS and increasing severity of phenotypic presentation (105–108). In this context, compared with even decades ago, anovulatory infertility may now be increased by obesity or visceral obesity due to sedentary/almost-immobile lifestyle and excess calorie intake. Overall, in prehistoric time or even a few decades ago when obesity was uncommon, women with the PCOS genotypes might have been protected from severe infertility, a situation reversed in the setting of the modern obesity epidemic.

Lessons from Ancestral and Derived Alleles of Candidate Gene Polymorphisms

It is very hard to test the aforementioned physiologic hypotheses based on fossil and remaining cultural artifact data. An alternate way to test possible selective advantages of a contemporary disease in our distant past is to focus on the genetic data related to the disease of interest. To show an effect on a disease, a gene must have more than one form (variation) in a population. Nucleotide changes at the DNA sequence level create these alternate forms of a gene, called “allele.” When a nucleotide change occurs, such as a change from C to T, owing to a mutation in a gene in a human population, the new allele T is called the “derived allele” and old C allele

is called the “ancestral allele.” Because the derived T allele was just formed, its frequency will be very low in the population, and it will also be called the “minor allele.” The most frequent ancestral allele will be called “major allele.” In successive generations, under the influence of selection or by chance (drift) the frequency of the new derived allele can increase in the population. Alternately, under the influence of selection or by chance it can disappear. There are millions of derived alleles in our genome. These are human lineage-specific changes that happened after the separation of humans from their most recent common ancestor with chimpanzees. Some of these alleles occurred early in the ancestors of humans. These types of relatively old derived alleles are usually found among all human groups around the globe and usually with highest frequencies in African populations, where humans originated. Some of these derived alleles can influence physiology, such as cold adaptation, and will be much more common in certain populations and reaching toward becoming the major allele. However, once-advantageous alleles can be risk factors for diseases in our contemporary societies, such as the alleles of genes associated with insulin resistance. Therefore, one way of deducing genetic changes leading to PCOS under selection is to compare the distribution of ancestral and derived alleles of candidate gene polymorphisms between PCOS case and control subjects. Table 1 presents the allelic nature and population frequency distribution of genetic variants associated with PCOS in multiple GWAS (40, 47, 51, 82, 97). From the first half of Table 1,

FIGURE 1



Evolutionary advantages and disadvantages of polycystic ovary syndrome (PCOS). From an evolutionary perspective, although susceptibility genes for PCOS may have constituted protective factors for human beings during prehistoric times, these inheritances would have turned into genetic triggers for complex metabolic diseases through changing lifestyle conditions.

Ünlütürk. Evolutionary determinants of PCOS. Fertil Steril 2016.

ancestral allele associations indicate that more than one-half of the derived alleles (5 of 9) that originated in the human lineage are risk factors for PCOS. Looking at derived (human lineage specific) alleles associated with PCOS, one can see that 11 out of 17 variants are associated with increased risk for PCOS. These individual SNP associations indicate that among the genes associated with PCOS, only 47% (9 out of 19 genes) had these increased risk allele changes in the human lineage. Moreover, the distribution of ancestral and derived alleles between protective and susceptible phenotypes is not statistically significant ($P > .5$) suggesting that PCOS susceptibility was not solely driven by a positive selection in human evolutionary history but already included genetic risk variants from their ancestors. Had PCOS conveyed a significant selective advantage for humans, the frequency of PCOS-associated genes with derived alleles should have been much higher.

Comparing the distribution of PCOS risk alleles among human populations, one can see that nearly all of the PCOS risk alleles are rather high frequency ($>10\%$) in human populations sampled from four different continents (Table 1), indicating lack of purifying selection on these risk alleles. Moreover, population genetic calculations based on published PCOS risk allele frequencies show that the homozygote risk genotype (presence of two risk alleles in the same individual) frequency in 13 out of 19 PCOS-associated genes is $>11\%$, a frequency rather similar to the 6%–19% PCOS prevalence rate reported in literature. This observation argues against any significant purifying (negative) selection on women (or men) with homozygote risk genotypes. Alternately, there should be either a strong heterozygote advantage or a balancing selection counteracting the effect of any negative selection acting on the risk alleles and genotypes. Indeed, a possible balancing selection on PCOS risk variants based on sexually antagonistic selection and intralocus conflict had been suggested (109, 110).

Interestingly, there are substantial allele frequency differences between populations. For example, the frequencies of PCOS risk alleles observed in *FSHR*, *C9orf3*, *LHCGR*, *FSHB*, *RAB5B/SUOX*, and *ERBB2* are much higher in non-African populations. On the other hand, the frequencies of PCOS-protective alleles observed in *DENND1A*, *SUMO1P1*, *GATA4/NEIL2*, *THADA*, *HMGA2*, *TOX3*, *INSR*, and *ERB4* are also higher in non-African populations. These observations suggest complex selective pressures, perhaps a balance of positive and negative factors, acting on PCOS-related genes under different environmental and cultural factors. Even if one can not exclude the role of genetic drift due to serial founder effects during ancient human migrations creating the observed allelic differences among populations (109), there is an ongoing active debate about this topic for PCOS (111). Clearly, more genetic research from different human populations is necessary to understand the evolutionary forces behind PCOS.

CONCLUSION

According to contemporary human genetic studies, PCOS may have persisted for more than 50,000 years. These find-

ings also support the idea that genetic triggers leading to PCOS might be candidate factors for the survival advantage of the human being (Fig. 1). Although natural selection can eliminate deleterious genes resulting in the harmful predisposition of the living organism, the persistence of susceptibility genes as a risk factor for metabolic diseases may be due to the fact that the rapid changes in human lifestyle may not have allowed enough time for any compensatory adaptation.

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