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Polymorphism T → C (−34 base pairs) of gene *CYP17* promoter in women with polycystic ovary syndrome is associated with increased body weight and insulin resistance: a preliminary study

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Abstract

The aim of this study was to establish the frequency of gene *CYP17* promoter polymorphism in women with polycystic ovary syndrome (PCOS) from a Chilean population and to examine the association of this polymorphism with body weight and estimate of insulin resistance in PCOS patient carriers and noncarriers of the A2 allelic variant. A total of 159 women with clinical and hormonal evidence of PCOS and 93 healthy women (HW) were evaluated. Diagnosis of PCOS was made according to the National Institutes of Health consensus criteria. In PCOS and HW, an oral glucose tolerance test was performed; and serum glucose and insulin were measured before the glucose load and 30, 60, 90, and 120 minutes after. Lipid profile and free fatty acid concentrations were determined in the basal sample. Insulin resistance was evaluated by homeostatic model assessment and insulin sensitivity index composite. A polymerase chain reaction–restriction fragment length polymorphism analysis was performed in all women to determine the A2 allele of the gene *CYP17* promoter. The genotype frequency was similar between HW and PCOS women. No differences in anthropometric measurements and metabolic parameters were observed in HW carrier and noncarrier of the A2 variant. In PCOS women, an increase in body mass index, waist circumference, homeostatic model assessment of insulin resistance, and fasting insulin according to the A2 allele dosage was observed ($P = .008$, $P = .016$, $P = .012$, and $P = .006$, respectively). Polycystic ovary syndrome patient carriers of the A2 allele with a body mass index greater than 29.9 kg/m^2 showed an odds ratio of 9.1 (confidence interval, 3.0-27.4; $P < .0001$) for developing insulin resistance. These data suggest that the frequency of the A2 allele is similar between PCOS patients and HW; however, the presence of this gene defect in PCOS patients seems to be associated with increase in body weight, abdominal adiposity, and metabolic components.

1. Introduction

In recent years, several studies have reported links between insulin resistance and polycystic ovary syndrome (PCOS), one of the most common endocrine disorders in premenopausal women, characterized by anovulatory infertility and hyperandrogenism [1-3]. In addition, most women with PCOS also exhibit peripheral insulin resistance, affecting predominantly muscle and adipose tissue, and a compensatory hyperinsulinemia independent of obesity [4-6]. At present, it is accepted that insulin resistance and pancreatic β-cell dysfunction, with increased risk of type 2 diabetes mellitus, are usual comorbidities in PCOS patients [7-9]. Approximately 50% of the PCOS women are overweight or obese, and most of them exhibit abdominal fat distribution [9]. Studies have shown that 25% to 35% of obese women with PCOS will have either impaired glucose tolerance or type 2 diabetes mellitus by 30 years of age and that the history of diabetes in a first-degree relative appears to define a subset of PCOS subjects with a greater prevalence of insulin secretory defects [10,11]. Therefore, PCOS is a major women's health issue with implications well beyond the reproductive endocrine abnormalities that usually bring women with PCOS to clinical attention in early ages. This

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offers the opportunity to detect metabolic abnormalities earlier in these women [7,12].

The evidence from family-based and association studies suggests that PCOS has a significant genetic basis, although the genes predisposing to PCOS have yet to be clearly defined. The candidate genes predisposing to PCOS include those involved in the regulation of ovarian steroidogenesis and also those genes that influence body mass index (BMI) and adiposity [13]. It has been proposed that an increased activity of ovarian P450c17α, a key enzyme in the biosynthesis of androgens, is the central disorder in the ovarian hyperandrogenism observed in this syndrome [14]. Therefore, the initial investigations focused on the possible role of *CYP17*, the gene that codes for cytochrome P450c17α, located on chromosome 10q24.3. A polymorphism has been found in the regulatory region of the *CYP17* gene, being a T to C substitution −34 base pairs (bp) from the translation initiation point in the promoter region (genotype A2/A2). It has been suggested that this change may up-regulate the expression of *CYP17*, resulting in an increased synthesis of androgens [15]. However, at present, no consistent association between this polymorphism and circulating androgen levels has been demonstrated [16-19]. On the other hand, in recent studies, this *CYP17* gene polymorphism has been linked with hyperinsulinemia and increased insulin secretion in patients with endometrial cancer [20] and has been proposed as a risk factor of tamoxifen-induced hepatic steatosis in breast cancer patients [21].

In this regard, it is possible that *CYP17* polymorphism could be associated with metabolic features of PCOS women, conferring some degree of susceptibility to obesity in these women more than hyperandrogenemia. Therefore, we investigated the frequency of the gene *CYP17* promoter polymorphism in a Chilean population and examined the association of this polymorphism with body weight and estimates of insulin resistance in PCOS patient carriers and noncarriers of the A2 allelic variant.

2. Subjects and methods

2.1. Subjects

One hundred fifty-nine unrelated women with PCOS, with an age range of 15 to 36 years, were consecutively recruited from patients attending the Unit of Endocrinology and Reproductive Medicine, University of Chile, between 2002 and 2006.

Diagnosis of PCOS was made if subjects had chronic anovulation and hyperandrogenism without any other specific causes of adrenal or pituitary disease and met the diagnostic criteria for PCOS of the National Institutes of Health consensus [22].

Inclusion criteria for cases were as follows: chronic oligo- or amenorrhoea, hirsutism, serum androstenedione concentration greater than 10.5 nmol/L, total testosterone concentration greater than 2.77 nmol/L, and/or free androgen index (FAI) greater than 6.0, according to cutoff values previously reported [23]. All women were amenorrheic and anovulatory according to progesterone measurements and ultrasound examination. The presence of characteristic ovarian morphology on ultrasound was not considered an inclusion criterion. Hyperprolactinemia, androgen-secreting neoplasm, Cushing syndrome, and attenuated 21-hydroxylase deficiency, as well as thyroid disease, were excluded by appropriate tests.

Table 1
Clinical and endocrine-metabolic parameters in HW and PCOS women

	HW (n = 93)	PCOS (n = 159)
Age (y)	24.6 ± 5.9	24.3 ± 5.8
BMI (kg/m^2)	25.5 ± 4.3	28.7 ± 6.1*
WC (cm)	81.8 ± 11.7	86.9 ± 14.1*
Fasting glucose (mmol/L)	4.5 ± 0.6	4.9 ± 0.6*
Fasting insulin (pmol/L)	79.4 ± 47.2	124.7 ± 93.8*
Androstenedione (nmol/L)	5.80 ± 3.2	12.0 ± 5.2*
Testosterone (nmol/L)	2.1 ± 1.0	3.1 ± 1.4*
SHBG (nmol/L)	59.2 ± 31.2	32.3 ± 19.2*
FAI	3.0 ± 1.9	13.8 ± 11.6*

Data are mean ± SD.
* $P < .05$, HW vs PCOS.

In addition, 93 healthy women (HW), with normal cycles and between 15 and 36 years of age, were included (Table 1). Each one had a history of regular 28- to 32-day menstrual cycles, absence of hirsutism and other manifestations of hyperandrogenism, and absence of galactorrhea and/or thyroid dysfunction. The women of the control group were recruited from community centers of the same geographical area as the patients and had the same socioeconomic level.

All women had given their written consent to their participation in the study that was approved by the local ethics committee.

2.2. Methods

After a 3-day 300-g carbohydrate diet and an overnight fast of 10 hours, all women were admitted to the Clinical Research Center in the morning (8:30 AM-9:00 AM). A clinical history was obtained, and a physical examination was conducted including anthropometric measurements. In PCOS and HW, a 75-g oral glucose tolerance test was done; and subjects were classified according to the World Health Organization criteria [24]. Serum glucose and insulin were measured before the glucose load and 30, 60, 90, and 120 minutes after. Sex hormone–binding globulin (SHBG), testosterone, androstenedione, lipid, and free fatty acid (FFA) concentrations were also measured before the glucose load. The FAI was calculated as the quotient of the molar concentrations of testosterone (in nanomoles per liter) and SHBG (in nanomoles per liter) (FAI = [testosterone/SHBG] × 100) [25].

2.3. Data analysis

The measurements derived from the oral glucose tolerance test included the following:

i) Serum fasting glucose, serum fasting insulin, homeostatic model assessment of insulin resistance (HOMA-IR) [26], and insulin sensitivity index (ISI) composite [27] to assess insulin resistance.
ii) To assess β-cell function, we used HOMA-B [26] and the insulinogenic index, calculated as the ratio of the increment in the serum insulin concentration to that in the serum glucose concentration during the first 30 minutes after the ingestion of glucose [28].
iii) Serum lipid profile, total cholesterol (TC), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C).
iv) Serum FFA concentrations.

2.4. Assays

Serum glucose was determined by the glucose oxidase method (Photometric Instrument 4010; Roche, Basel, Switzerland). The coefficient of variation of this method was less than 2.0%. Serum insulin and testosterone were assayed by radioimmunoassay (Diagnostic System Laboratories, Webster, TX), androstenedione was assayed by radioimmunoassay (Diagnostic Products, Los Angeles, CA), and SHBG was determined by radioimmunometric assay (Diagnostic Products). The intra- and interassay coefficients of variation were 5% and 8% for insulin, 7.0% and 11.0% for testosterone, 3.7% and 4.9% for androstenedione, and 5.3% and 7.9% for SHBG. The lipid profile was determined by standard colorimetric assays (Photometric Instrument 4010, Roche). The coefficient of variation of this method was less than 3.0%. Serum FFAs were determined by colorimetric assay (Biovision Research Products, Mountain View, CA). The intra- and interassay coefficients of variation for this method were 4% and 6%, respectively.

2.5. Anthropometric measurements

Anthropometric measurements were performed in all subjects. Height was measured to the nearest 0.1 cm using a wall-mounted stadiometer; weight was measured to the nearest 0.1 kg using a hospital balance beam scale. *Body mass index* was used as a measure of overall adiposity and was defined as weight (in kilograms)/height^2 (in square meters). The category of body weight (normal, overweight, or obese) was defined by the World Health Organization criteria [29]. Waist circumference (WC) was measured to the nearest 0.5 cm at the point of narrowing (as viewed from behind) between the umbilicus and xiphoid process.

2.6. Molecular analysis

Genomic DNA was extracted from peripheral blood leukocytes. Polymorphism T → C (−34 bp) of the gene *CYP17* promoter (defined as the A1 and A2 alleles) was determined by polymerase chain reaction and restriction fragment length polymorphism using *Msp*AI endonuclease digestion, as previously described [17]. A subset of 100 random samples from the study population was double genotyped in a blinded fashion with concordant results. The error in genotyping was 1.0%.

2.7. Statistical evaluation

Data are expressed as mean ± standard deviation (SD). Differences among study groups were assessed through Student *t* test or 1-way analysis of variance when data were normally distributed, and Mann-Whitney test or Kruskal-Wallis test when data were not normally distributed. In all cases, the Bonferroni correction for multiple comparisons was performed. Multiple regression techniques were performed to assess the effect of BMI or fasting insulin in the association of A2 allele with anthropometric measurements or metabolic parameters. The T → C (−34 bp) polymorphism was transformed to a dichotomous variable and used as the independent variable. The anthropometric measurements and metabolic parameters were used as the dependent variable, and BMI or insulin was used as covariate. The association in categorical variables was calculated by χ^2. The odds ratio (OR) values were assessed by logistic regression techniques. Odds ratios and 95% confidence intervals (CIs) for the BMI effects of the different genotypes on the development of PCOS were calculated by taking into account the effects of the interaction term between BMI and the genotype. The effect of obesity was evaluated using a cutoff value of greater than 29.9 kg/m^2 for BMI. Hardy-Weinberg equilibrium was evaluated through an exact method. Statistical analysis was performed with the STATA 7.0 (StataCorp, College Station, TX) package. Power calculations were performed using the program of Purcell et al [30] (http://pngu.mgh.harvard.edu/purcell/gpc/). Assuming a prevalence of insulin resistance in PCOS patients of 70% (119 PCOS patients with insulin resistance and 40 PCOS patients without insulin resistance), a minor allele frequency of 30%, and a type I error of 0.05, we estimate power for a generalized risk factor as 94.0% to detect a relative risk (RR) of 1.3 for A1/A2 allele and RR of 1.8 for A2/A2. The significance level was set at 5%.

3. Results

Table 1 shows the clinical and hormonal characteristics of HW and PCOS women. Mean age was not different between HW and PCOS women. Body mass index was significantly higher in PCOS women compared with HW ($P < .0001$). As expected, WC ($P = .002$), serum androstenedione concentrations ($P < .0001$), total serum testosterone concentrations ($P < .0001$), and FAI ($P < .0001$) were significantly higher and SHBG ($P < .0001$) was significantly lower in PCOS women compared with HW. Moreover, PCOS women showed significantly higher fasting glucose, insulin concentrations, and FFA than control women ($P < .0001$). These differences remained significant after adjusting by BMI ($P < .05$), except for WC ($P = .105$). Those whose BMI was greater than 29.9 kg/m^2 represented 9.7% of HW and 39.0%

of PCOS women ($P < .001$). The prevalence of impaired glucose tolerance was 1.1% in HW and 10.6% in PCOS women ($P = .02$). Thirty percent of HW and 74.8% of PCOS women exhibited insulin resistance according to a HOMA-IR value of 2.4 (mean ± 2 SD from HW with normal weight). Similar results were obtained with a cutoff value of 6.0 for ISI composite (HW: 38.2% and PCOS: 74.8%, $P < .001$)

Genotype frequency was not different between HW and PCOS women (A1/A1: 0.46 vs 0.37, A1/A2: 0.39 vs 0.51, and A2/A2: 0.15 vs 0.12, respectively; $P = .171$). The frequency for the A2 allele was 0.37 in PCOS women and 0.34 in HW ($P = .340$). Both groups were in Hardy-Weinberg equilibrium ($P = .269$ and $P = .170$). Logistic regression analysis adjusted by A2 carriers and BMI showed an association between PCOS and the A2 variant (OR, 1.02; 95% CI, 1.00-1.04; $P = .012$). On the other hand, adjusting by A2 carriers and BMI greater than 29.9 kg/m^2, a strong association between PCOS and the A2 variant was observed (OR, 6.5; 95% CI, 2.6-15.8; $P < .0001$).

The metabolic parameters of HW carriers and noncarriers of the A2 allele are shown in Table 2. No differences in anthropometric measurements and metabolic parameters were observed in HW carrier and noncarrier of the A2 allele.

In PCOS women, an increase in BMI, WC, and HOMA-IR according to the A2 allele dosage was observed ($P = .008$, $P = .016$, and $P = .012$, respectively) (Fig. 1A-C). Similar observation was found in fasting insulin concentration (A1/A1: 98.0 ± 59.0 pmol/L, A1/A2: 138.3 ± 111.2 pmol/L, and A2/A2: 147.3 ± 82.7 pmol/l; $P = .006$). In addition, carriers of the A2/A2 genotype showed higher BMI ($P = .001$, Bonferroni corrected = .01), WC ($P = .001$, Bonferroni corrected = .01), and HOMA-IR ($P = .008$, Bonferroni corrected = .08) compared with carriers of the A1/A1 genotype (Fig. 1A-C). Moreover, carriers of the A1/A2 genotype exhibited higher BMI ($P = .006$, Bonferroni corrected = .06) and waist diameter ($P = .043$, Bonferroni corrected = .43) compared with A1/A1 carriers.

Table 2
Clinical and endocrine-metabolic parameters of HW carriers and noncarriers of the A2 allele

	HW (A1/A1) (n = 43)	HW (X/A2) (n = 50)
BMI (kg/m^2)	25.4 ± 4.3	25.7 ± 4.3
WC (cm)	81.6 ± 10.6	81.9 ± 12.7
Fasting		
Glucose (mmol/L)	4.4 ± 0.6	4.5 ± 0.7
Insulin (pmol/L)	70.0 ± 43.6	87.3 ± 71.8
HOMA-IR	1.8 ± 1.2	2.4 ± 2.3
HOMA-B	290.2 ± 331.9	288.1 ± 190.6
Insulinogenic index	3.2 ± 6.6	3.3 ± 7.1
FFA (mmol/L)	0.6 ± 0.2	0.7 ± 0.3
TG (mmol/L)	1.4 ± 0.6	1.2 ± 0.7
TC (mmol/L)	4.6 ± 0.9	4.4 ± 0.9
HDL-C (mmol/L)	1.1 ± 0.2	1.1 ± 0.3
2 h		
Glucose (mmol/L)	4.5 ± 1.4	4.9 ± 1.2
Insulin (pmol/L)	279.2 ± 222.9	318.8 ± 299.3
ISI composite	8.2 ± 5.8	7.1 ± 4.6

Data are mean ± SD.

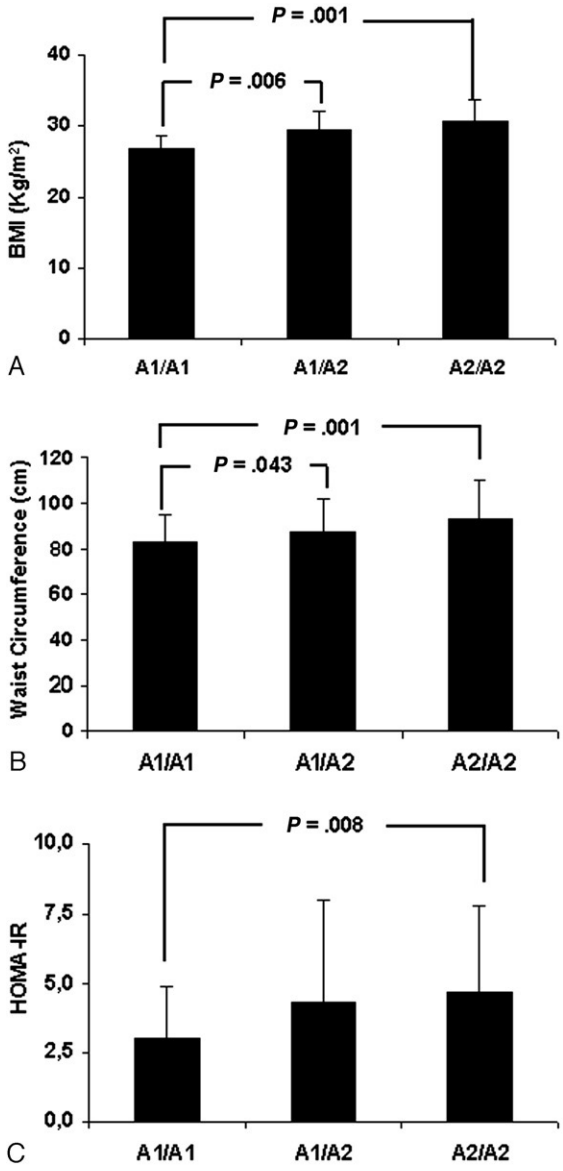

Fig. 1. Body mass index, WC, and fasting insulin according to CYP17 genotype categories in PCOS women. *P* values are *unadjusted*.

The metabolic parameters of PCOS women carriers and noncarriers of the A2 allele are shown in Table 3. The PCOS women carriers of A2 allele exhibited higher BMI ($P = .001$, Bonferroni corrected = .014), WC ($P = .011$, Bonferroni corrected = .154), fasting insulin ($P = .003$, Bonferroni corrected = .042), HOMA-B ($P = .022$, Bonferroni corrected = .308), 2-hour insulin ($P = .005$, Bonferroni corrected = .070), and FFAs ($P = .0001$, Bonferroni corrected = .001) compared with PCOS noncarriers. These differences became not significant after adjusting by BMI. However, the association between carriers of the A2 allele and BMI remained significant after adjusting by fasting insulin ($P = .03$).

Table 3
Clinical and endocrine-metabolic parameters of PCOS women carriers and noncarriers of the A2 allele

	PCOS (A1/A1) (n = 59)	PCOS (X/A2) (n = 100)
BMI (kg/m^2)	26.8 ± 4.4	29.8 ± 6.7*
WC (cm)	83.7 ± 11.2	88.7 ± 15.2*
Fasting		
Glucose (mmol/L)	4.8 ± 0.6	4.9 ± 0.7
Insulin (pmol/L)	98.3 ± 59.3	141.0 ± 106.1*
HOMA-IR	3.0 ± 1.9	4.5 ± 3.6*
HOMA-B	310.0 ± 331.6	356.3 ± 288.2*
Insulinogenic index	2.3 ± 1.9	2.7 ± 3.6
TG (mmol/L)	1.3 ± 0.5	1.5 ± 0.8
TC (mmol/L)	4.9 ± 1.0	4.9 ± 1.3
HDL-C (mmol/L)	1.1 ± 0.2	1.0 ± 0.3
FFA (mmol/L)	0.7 ± 0.2	0.9 ± 0.3*
2 h		
Glucose (mmol/L)	5.6 ± 1.3	6.1 ± 1.6
Insulin (pmol/L)	526.6 ± 419.1	751.2 ± 726.9*
ISI composite	5.2 ± 3.5	4.3 ± 3.2

Data are mean ± SD.
* $P < .05$, PCOS carriers vs PCOS noncarriers.

In PCOS women, logistic regression analysis showed that the A2 allele was associated with a BMI greater than 29.9 kg/m^2 (OR, 3.4; 95% CI, 1.6–7.1; $P = .001$) and insulin resistance (OR, 2.4; 95% CI, 1.2–4.9; $P = .016$). Moreover, carriers of the A2 allele with a BMI greater than 29.9 kg/m^2 showed an OR of 9.1 (CI, 3.0-27.4; $P < .0001$) for developing insulin resistance.

In relation to androgen concentration, serum testosterone (3.3 ± 1.7 vs 3.4 ± 1.5 nmol/L, $P = .700$) and androstenedione (12.3 ± 5.6 vs 11.9 ± 4.4 nmol/L, $P = .618$) were similar between PCOS noncarriers and PCOS carriers of the A2 allele. On the other hand, taking all PCOS patients together, a positive correlation between fasting insulin and testosterone concentrations was observed ($r = 0.172$, $P = .047$). Although PCOS carriers of the A2 variant did not exhibit significantly higher testosterone concentrations compared with PCOS noncarriers, the positive correlation between fasting insulin and testosterone remained significant in patient carriers of the A2 variant ($r = 0.235$, $P = .029$), which was not observed in noncarriers.

4. Discussion

In the present study, we examined the prevalence of a polymorphism of the gene *CYP17* promoter (A2 variant) in a Chilean population of PCOS women and the relationship of the A2 variant with metabolic features of PCOS. We found a similar frequency of the A2 allele in HW and PCOS women. The presence of this gene defect in PCOS patients was associated with increase in BMI and insulin resistance. Therefore, an interaction between the effect of this variant and body weight in PCOS seems to be possible.

This *CYP17* promoter gene polymorphism has been reported in other populations. In Greek populations, Diamati-Kandarakis et al [17] described the different *CYP17* genotypes in 50 patients with PCOS and 50 HW. In PCOS women, they observed a similar distribution of genotypes compared with our study. However, in control women, the homozygosity of the polymorphic A2 allele was not observed, which differs from the results of the present study in which 15% of controls exhibited the A2/A2 genotype.

In the present study, the frequency of the A2 allele was similar in HW and PCOS women, which is in agreement with previous studies [16,31]. The allelic frequency of the A2 allele was similar in the Chilean population (37% for PCOS and 34% for HW) and the white population of the study by Gharani et al [16] (44% for PCOS and 34% for HW).

Preliminary case-control data suggested an association between the variant allele of *CYP17* and PCOS [15]. These findings were, however, based on a relatively small population of subjects; and subsequently, the present and other studies [16-18,32] have been unable to confirm these results. Moreover, recently, Marszalek et al [31] demonstrated that the polymorphic A2 allele is no more frequent in women with PCOS than in HW. Similarly, in the present study, we could not find an association between the A2 allele and PCOS, probably because the sample size was too small to detect an association between these 2 variables. Using the Genetic Power Calculator program [30] with our sample size and considering an 80% genetic power, we could eventually detect a genotype RR of 2.5 or more, which is much higher than the one expected for a disease like PCOS, which would be near 1.3. Therefore, our study is clearly underpowered to detect such a risk. However, this was not the aim of the current investigation.

To obtain a 20% difference in the testosterone levels between the carriers and noncarriers of the A2 allele, considering a power of 80%, the sample size required is 113 subjects. In the present study, we have analyzed 159 subjects; so there is enough power to compare testosterone levels between the 2 groups. Hormonal profiles were not significantly different between carriers of A1/A1 allele and carriers of A1/A2 and A2/A2 alleles within the PCOS group. Therefore, it is possible to conclude that the T → C polymorphism of the *CYP17* gene is not associated with the steroid hormone synthesis in PCOS. Nevertheless, in the present study and in concordance with previous reports in PCOS women, a positive correlation between testosterone and insulin serum concentration was observed [33,34], suggesting that hyperinsulinemia could induce an increase in the expression and enzymatic activity of P450c17 [35,36]. In this regard, we observed that, although PCOS carriers of the A2 variant did not exhibit significantly higher testosterone concentrations compared with PCOS noncarriers, the positive correlation between fasting insulin and testosterone remained significant in patient carriers of the A2 variant, suggesting that, in this group, hyperinsulinemia may promote an increase in the activity of P450c17.

Recently, *CYP17* gene polymorphism has been associated with metabolic conditions [20,21]. In the present study, PCOS carriers of A2 allele presented a greater BMI and WC than PCOS noncarriers. Moreover, estimates of insulin resistance were significantly different in PCOS carriers compared with PCOS noncarriers. Although we observed an increase in 3 units of BMI between carriers and noncarriers of allele A2, this represents a difference of approximately 10% in the body weight of these women, which could worsen the PCOS conditions in women carriers of allele A2, considering that a modest weight loss of 5% body weight has been shown to result in significant improvements in both symptoms of hyperandrogenism and ovulatory function in women with PCOS [37,38].

Relatively recently, the expression and enzymatic activity of the P450c17 gene in human adipose tissue have been described [39], representing an additional source of androgens that could be associated with insulin resistance. It has been demonstrated that there is a marked increase in catecholamine-induced lipolysis within visceral adipocytes isolated from nonobese women with PCOS compared with BMI-matched control women [40]. On the other hand, studies on healthy men and women have demonstrated that testosterone may facilitate nonesterified fatty acid release from visceral adipocytes in vivo [41,42]. In this regard, it has been suggested that, in women with PCOS, the development of android adiposity, which is strongly related to insulin resistance [23], results at least in part from the effect of hyperandrogenemia on the adipocyte [13].

We speculate that the presence of this polymorphism may increase local androgen production, leading to enhanced visceral adipocyte lipolysis and to higher release of nonesterified fatty acid from adipocytes, which may enhance hepatic gluconeogenesis and reduce insulin extraction and peripheral glucose uptake, thereby leading to insulin resistance and a secondary increase in BMI [42,43]. This assumption is based on the fact that PCOS carriers are more obese, exhibit more abdominal fat, and have higher FFA concentrations, suggesting that, in PCOS carriers, an interaction between the effect of this variant and the abdominal adiposity of the PCOS condition seems to be possible. Nevertheless, in the present study, it is interesting to note that the OR for developing insulin resistance increases in obese PCOS patient carriers of the A2 allele. Moreover, according to covariate analysis, the insulin association became nonsignificant when adjusted for BMI; but the BMI effect remained significant when adjusted for insulin. Therefore, the data suggest that local androgen production may affect mass or accumulation of adipose tissue. As adiposity increases, fasting insulin increases as a consequence. Independently, if BMI or insulin resistance is primarily affected by the A2 variant of *CYP17*, a relationship between this polymorphism and metabolic derangements could be established. Thus, we propose that the *CYP17* gene polymorphism is a modifier gene, a situation that is usual in complex diseases.

In this preliminary study, differences in metabolic parameters were detected between PCOS women carriers and noncarriers of the A2 allele. However, the sample size was relatively small; therefore, further studies with a greater number of cases and with more sophisticated methods are necessary to confirm these findings.

In conclusion, the prevalence and genotype distribution of *CYP17* polymorphism between HW and PCOS women in the female Chilean population are comparable to previous studies. No relationship was found between the *CYP17* variant and serum androgen levels. However, in the present study, this variant appears to be associated with the metabolic component and obesity of the PCOS condition.

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