Small glutamine-rich tetratricopeptide repeat-containing protein alpha (SGTA), a candidate gene for polycystic ovary syndrome

M.O. Goodarzi1,2,3,4, N. Xu1, J. Cui3, X. Guo3, Y.I. Chen2,3,4 and R. Azziz2,4,5,6

1Division of Endocrinology, Diabetes and Metabolism, Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, CA 90048, USA; 2Department of Obstetrics and Gynecology, Center for Androgen Related Disorders, Cedars-Sinai Medical Center, Los Angeles, CA 90048, USA; 3Medical Genetics Institute, Cedars-Sinai Medical Center, Los Angeles, CA 90048, USA; 4Department of Medicine, the David Geffen School of Medicine at UCLA, Los Angeles, CA 90095, USA; 5Department of Obstetrics and Gynecology, the David Geffen School of Medicine at UCLA, Los Angeles, CA 90095, USA; 6Correspondence address. Tel: +1-310-423-7433; Fax: +1-310-423-3470; E-mail: azzizr@cshs.org

BACKGROUND: Polycystic ovary syndrome (PCOS) is a heterogenic, complex common genetic disease. Multiple pathways are involved in its pathogenesis, including the androgen signaling pathway and insulin signaling pathway. Small glutamine-rich tetratricopeptide repeat-containing protein alpha (SGTA) is a putative member of the androgen receptor–chaperone–co-chaperone complex, and may play a role in androgen signaling as a co-chaperone. Polymorphisms in the SGTA gene have not been evaluated for a role in PCOS. METHODS: Women with and without PCOS (287 cases, 187 controls) were genotyped for three single nucleotide polymorphisms (SNPs) in SGTA. SNPs and haplotypes were determined and tested for association with PCOS and component traits of PCOS. RESULTS: For SNP rs1640262, homozygotes for the minor allele were protected against PCOS ($P = 0.009$). Haplotype 1 (G–A–T) was associated with increased risk of PCOS ($P = 0.015$). In women with PCOS, haplotype 2 (A–G–C) was associated with increased insulin resistance ($P = 0.013$), consequently resulting in increased insulin secretion ($P = 0.014$). CONCLUSIONS: This study presents genetic evidence suggesting a potential role of SGTA in the pathogenesis of PCOS. SGTA may provide a connection between multiple pathways in PCOS.

Keywords: polycystic ovary syndrome; small glutamine-rich tetratricopeptide repeat-containing, alpha; single nucleotide polymorphism; haplotype; association

Introduction

Polycystic ovary syndrome (PCOS) is a heterogenic, complex common genetic disease, affecting $\sim 6\% - 8\%$ of reproductive age women (Azziz et al., 2004). PCOS is characterized by hyperandrogenism, menstrual dysfunction and polycystic ovarian morphology (Goodarzi and Azziz, 2006). Patients with PCOS may also present with infertility, obesity, insulin resistance and often have a high burden of cardiovascular risk factors.

The molecular basis for PCOS is poorly understood. Candidate genes for PCOS have been chosen from logical pathways, such as the insulin signaling pathway or androgen biosynthetic pathway (Franks and McCarthy, 2004; Escobar-Morreale et al., 2005; Nam Menke and Strauss, 2007; Urbanek, 2007). Hypotheses regarding these pathophysiologic pathways have led to the implication of several genes in the development of PCOS. However, since PCOS is a complex common disease, which is likely due to both genetic and environmental factors, more evidence is needed to explain the molecular mechanisms of PCOS.

Although the etiology of PCOS remains unknown, most patients with PCOS present with hyperandrogenism. The phenotype of PCOS may have hirsutism and ovulatory dysfunction without significantly increased androgens (Azziz et al., 2005). Up to 25% of PCOS patients have normal levels of circulating androgens, which suggests sensitivity to androgens is increased in this type of PCOS (Chang et al., 2005). Even in those with hyperandrogenemia, the degree of androgen elevation is typically mild. Therefore, components of androgen signaling may play a key role in the pathophysiology of PCOS, in some or all subjects. Unbound androgen receptor (AR) is inactive in the cytoplasm as a large dynamic heterocomplex which is composed of heat shock proteins (such as Hsp70 and Hsp90) and their co-chaperones (Pratt and Toft, 1997). Three main families of co-chaperones include Bag-1 homology (Bcl-2 binding athanogene or Bag domains), Dnaj homology (or J domains) and...
Materials and Methods

Subjects

A total of 287 consecutive White patients with PCOS, aged 13–47 years, and 187 healthy White control women, aged 14–60, were recruited from Birmingham, AL, USA. All subjects were unrelated. PCOS subjects were recruited consecutively from the reproductive endocrine practice of one of the investigators (R.A.) at the University of Alabama at Birmingham (UAB). Participation in research studies was offered to patients meeting inclusion criteria (premenopausal, non-pregnant, on no hormonal therapy, including oral contraceptives, for at least 3 months, and meeting diagnostic criteria for PCOS). In order to ensure the inclusion of women with the classic disorder, the presence of PCOS was defined by the 1990 National Institutes of Health consensus criteria (Zawadzki and Dunai, 1992), including: (i) clinical hyperandrogenism and/or hyperandrogenemia, (ii) oligo-ovulation and (iii) the exclusion of related disorders, including androgen-producing tumors, non-classic 21-hydroxylase-deficient adrenal hyperplasia, hyperprolactinemia, active thyroid disease or Cushing’s syndrome. The specific parameters for defining hirsutism, hyperandrogenemia, ovulatory dysfunction and exclusion of related disorders were previously reported (Azziz et al., 2004).

Controls were healthy women, with regular menstrual cycles or a history of regular menstrual cycles before menopause, and without family history of hirsutism. These women had no evidence of hirsutism, acne, or alopecia, or endocrine dysfunction and had not taken hormonal therapy (including oral contraceptives) for at least 3 months prior to testing. Controls were recruited by word of mouth and advertisements in Birmingham, AL, through a call for ‘healthy women’ without detailing further the nature of the studies.

All subjects gave written informed consent, and the study was performed according to the guidelines of the Institutional Review Boards of UAB and Cedars-Sinai Medical Center.

Phenotyping

Subjects underwent a brief physical examination, hirsutism scoring using a modification of the Ferriman–Gallwey method (Hatch et al., 1981), and underwent blood sampling. Hormonal measures, including total and free testosterone, dehydroepiandrosterone sulfate (DHEAS), 17α-hydroxyprogesterone (17-HP) and sex hormone-binding globulin (SHBG), were obtained between Days 3 and 8 (follicular phase) following a spontaneous menstrual cycle or progesterone-induced withdrawal bleed, as described (Azziz et al., 2004). Total testosterone was measured after serum extraction by an in-house radioimmunoassay (RIA) method, SHBG activity was measured by competitive binding analysis, using Sephadex G-25 (Sigma-Aldrich Corp., St Louis, MO, USA) and [3H]testosterone as the ligand and the free testosterone was calculated as previously described (Pearlman et al., 1967; Boots et al., 1998). The SHBG method gives values of ~100–300 nmol/l in normal adult women. DHEAS and 17-HP were measured by direct RIA using commercially available kits (from Diagnostic Products Corp., Los Angeles, CA, USA). The intra- and inter-assay variations for the hormonal assays have been previously reported (Knochenhauer et al., 1998). The same laboratory assays were employed for all subjects. For these androgen-related traits measured in the women with PCOS, completeness of data was over 98%. The total and free testosterone values of three cases were statistical outliers; therefore, these values were deleted from analysis.

Fasting glucose and insulin were also obtained in a subset of the cohort (~70%). The computer-based homeostasis model assessment (HOMA, www.dtu.ox.ac.uk/homa) utilizes fasting glucose and insulin to calculate indices of insulin resistance (HOMA-IR) and insulin secretion (HOMA-%B) (Levy et al., 1998; Wallace et al., 2004). An ideal, normal-weight person <35 year of age has a HOMA-IR = 1 and HOMA-%B = 100% (Matthews et al., 1985). For the insulin-related traits only, subjects with diabetes (n = 6) were excluded because the hyperglycemia of diabetes may induce secondary changes in insulin-related traits that reduce their utility for genetic analyses.

Genotyping and haplotype determination

We selected three SNPs, rs2238614, rs741103 and rs1640262, which span the 28.6 kb genomic length of SGTA. These were selected because they are predicted to tag the haplotypes (across the entire gene, plus 2 kb upstream) occurring at >1% frequency in the Caucasian population of the HapMap database (The International HapMap Consortium, 2003). The three SNPs were genotyped using the 5'-exonuclease assay (TaqMan MGB, Applied Biosystems, Foster City, CA, USA) described previously (Livak, 1999; Goodarzi et al., 2003); duplicate genotyping of 96 samples for one SNP yielded 100% concordance. The PCR primers and TaqMan MGB probes are presented in Table I. The genotyping success rate was 94.4%.
Haploview 3 (Barrett et al., 2005) was used to determine haplotypes as well as haplotype blocks. Haploview constructs haplotypes using an accelerated expectation maximization algorithm similar to the partition/ligation method (Qin et al., 2002). Haploview was used to calculate linkage disequilibrium (LD, the \( D' \) statistic and \( r^2 \)) between each pairwise combination of SNPs. Haploview is able to determine haplotype blocks using different block partition algorithms or user-defined blocks (Barrett et al., 2005). As the various algorithms gave slightly different haplotype blocks, we chose to consider a block spanning the entirety of the gene. Haplotypes were assigned to individual subjects only when the assignment could be made with a >95% certainty.

**Statistical analysis**

For all analyses, quantitative trait values were log- or square root-transformed as appropriate to reduce non-normality. Unpaired \( t \)-tests and chi-square tests were used to compare clinical characteristics between women with and without PCOS. Quantitative data are presented as median (inter-quartile range).

Association of SNPs or haplotypes with presence/absence of PCOS was evaluated using logistic regression, adjusting for BMI and age. Association with quantitative phenotypic variables utilized analysis of covariance, again adjusting for age and BMI.

To confirm any significant associations, we estimated empirical \( P \)-values by permutation analysis. For each significant association, the samples were permuted by shuffling genotypic data 1000 times, and subsequent association analyses were carried out to obtain the distribution of the test statistic under the null hypothesis of no association. The empirical \( P \)-values were obtained as the proportion of the 1000 replicates that had a \( P \)-value less than or equal to the nominal ones obtained from the actual (unshuffled) data. These empirical \( P \)-values are reported in the Results.

As a further measure to handle multiple testing, significance was taken at \( P < 0.017 \), considering that we analyzed one LD group of SNPs against three families of traits (PCOS diagnosis, androgens and metabolic traits), yielding a correction factor of three (i.e. three independent comparisons). Analyses were carried out using Statview 5.0 (SAS Institute, Cary, NC, USA).

### Results

**Clinical characteristics of the study cohort are shown in Table II.** We genotyped three SNPs spanning the *SGTA* gene (Table III and Fig. 1). LD \( (D') \) among the SNPs in our subjects ranged from 0.70 to 0.99, with an average \( D' \) of 0.81. The \( r^2 \) ranged from 0.36 to 0.91 (average 0.55). The overall high degree of LD confirmed the possibility of constructing haplotypes across the entire gene. Table IV displays the *SGTA* haplotypes and their frequencies. The haplotypes observed in our White subjects matched those predicted for Caucasians in HapMap, differing only moderately in frequency. The three haplotypes of frequency >5% were tested for association with PCOS and its component traits.

**Homzygotes for the minor allele of SNP rs1640262 were protected against PCOS, with an age- and BMI-adjusted odds ratio (OR) of 0.18 [95% confidence interval (CI) 0.039–0.82, \( P = 0.009 \)]. Haplotype 1 (the most common haplotype), G–A–T, was associated with increased risk of PCOS, with an age- and BMI-adjusted OR of 4.12 [95% CI 1.20–14.10, \( P = 0.015 \)]. SNP rs1640262 and haplotype 1 were not associated with quantitative component traits (see Supplementary Tables I–IV for trait medians by genotype).

In women with PCOS, haplotype 2 (A–G–C, second most common haplotype) was associated with increased insulin resistance [HOMA-IR: haplotype 2 carriers: 2.19 (2.00); \( P = 0.013 \)], and also associated with increased insulin secretion [HOMA-%B, haplotype 2 carriers: 2.19 (2.00); \( P = 0.013 \)]. No associations were observed with the other quantitative traits in women with PCOS. No quantitative trait associations were obtained in case.

<table>
<thead>
<tr>
<th>Variant</th>
<th>PCR primers</th>
<th>TagMan MGB probes</th>
</tr>
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<tbody>
<tr>
<td>rs2238614</td>
<td>GGAACCTTTTATGGCAGACACCTTA</td>
<td>CGCCCTCGGGGTCT</td>
</tr>
<tr>
<td>rs741103</td>
<td>TGGCACAAGCTACATGGAACACAGGGCGAGCTTTG</td>
<td>AGCCTTCCGGCTAGCACG</td>
</tr>
<tr>
<td>rs1640262</td>
<td>AACCAGCCCCAGCTGTA</td>
<td>ACAGGCGGAGACAGGACGTT</td>
</tr>
<tr>
<td></td>
<td>TCCAGCGCTTTCCGCTCATTT</td>
<td>ATCTAGCAGGCCACAC</td>
</tr>
</tbody>
</table>

Primers for PCR are listed 5’ to 3’ and were synthesized by Invitrogen (Carlsbad, CA, USA). Primers were listed 5’ to 3’ and were synthesized by Applied Biosystems. The probes are labeled at the 5’ end with 6FAM or VIC (laser-activated fluorescent dyes), and at the 3’ end with a quencher/minor groove binder.

<table>
<thead>
<tr>
<th>Table II.</th>
<th>Clinical characteristics of the study group.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control (( n = 187))</td>
</tr>
<tr>
<td>Age (year)</td>
<td>33.0 (17.0)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.1 (6.4)</td>
</tr>
<tr>
<td>WHR</td>
<td>0.78 (0.08)</td>
</tr>
<tr>
<td>mFG score</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hirsute (%)</td>
<td>0</td>
</tr>
<tr>
<td>Total testosterone (nmol/l)</td>
<td>1.42 (0.92)</td>
</tr>
<tr>
<td>Free testosterone (pmol/l)</td>
<td>12.1 (9.0)</td>
</tr>
<tr>
<td>DHEAS (μmol/l)</td>
<td>2.58 (2.03)</td>
</tr>
<tr>
<td>SHBG (nmol/l)</td>
<td>220.0 (120.0)</td>
</tr>
<tr>
<td>Insulin (pmol/l)</td>
<td>49.5 (45.9)</td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td>4.77 (0.56)</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>0.92 (0.83)</td>
</tr>
<tr>
<td>HOMA-%B</td>
<td>103.9 (59.5)</td>
</tr>
</tbody>
</table>

Data are median (inter-quartile range). * \( P < 0.001 \) compared with control group, by unpaired \( t \)-tests or chi-square tests as appropriate; quantitative data were transformed to approximate normality.

WHR, waist to hip ratio; mFG: modified Ferriman–Gallwey; DHEAS, dehydroepiandrosterone sulfate; SHBG, sex hormone-binding globulin; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-%B, homeostasis model assessment of insulin secretion.

**Table I.** Primers and probe sequences used in the 5’-exonuclease assay of the small glutamine-rich tetratricopeptide repeat containing protein alpha (*SGTA*) gene.
SGTA is candidate gene for polycystic ovary syndrome

Table III. Frequency and location information on SGTA variants.

<table>
<thead>
<tr>
<th>Variant Designation</th>
<th>Alleles (major/minor)</th>
<th>Location</th>
<th>Overall MAF</th>
<th>PCOS MAF</th>
<th>Control MAF</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs2238614</td>
<td>G/A</td>
<td>Exon 14 (3'UTR)</td>
<td>0.195</td>
<td>0.168</td>
<td>0.237</td>
</tr>
<tr>
<td>rs741103</td>
<td>A/G</td>
<td>Intron 1</td>
<td>0.150</td>
<td>0.135</td>
<td>0.173</td>
</tr>
<tr>
<td>rs1640262</td>
<td>T/C</td>
<td>Intron 1</td>
<td>0.208</td>
<td>0.183</td>
<td>0.249</td>
</tr>
</tbody>
</table>

MAF, minor allele frequency; UTR, untranslated region.

Figure 1: Gene structure and LD plot for small glutamine-rich tetra-tricopeptide repeat containing protein alpha (SGTA). The gene structure of SGTA is shown at top; the gene has 14 exons (represented by vertical bars) and is located on the reverse strand of chromosome 19 (19p13.3). The locations of the genotyped SNPs relative to the exons are indicated. The linkage disequilibrium plot at the bottom displays $D'$ values (%) for each pair of SNPs in the box at the intersection of the diagonals from each SNP. The SNPs were considered together in one haplotype block as indicated.

Discussion
This is the first study evaluating association of variants in the SGTA gene with PCOS. Homozygotes for the minor allele of SNP rs1640262 were protected against PCOS. Haplotype 1 was associated with increased risk of PCOS. Haplotype 2 was associated with increased insulin resistance, and consequently increased beta cell function. SGTA was initially selected based on its probable role in androgen signaling, which has recently been verified experimentally (Buchanan et al., 2007).

Hyperandrogenemia due to excessive ovarian and adrenal androgen production is widely regarded as the predominant feature of PCOS (Rosenfield, 1999). Even PCOS patients with biochemical normoandrogenemia may have increased androgen levels at both the systemic and the tissue level, albeit not consistently detectable in the laboratory evaluation. To evaluate the responsiveness or sensitivity of the AR at the cellular level, it is a prerequisite to estimate the concentrations of androgens (its specific ligand) acting upon the receptor. However, this estimate is precluded by our inability to measure serum androgen levels accurately, as well as by the fact that circulating androgen levels do not equate to local tissue levels. In any case, the degree of hyperandrogenemia in PCOS is typically not severe. With this in mind, we believe androgen hypersensitivity may play an important contributing role in the development of PCOS. Indeed, there is already some genetic evidence to support this hypothesis: specifically, associations of 5-alpha reductase and AR gene variants with PCOS (Hickey et al., 2002; Goodarzi et al., 2006).

The SGTA protein has 313 amino acids and contains three TPR motifs in tandem. The TPR domain, which mediates protein–protein interactions, is a degenerate 34-amino acid motif, containing eight loosely conserved consensus residues: W–L–G–Y–A–F–A–P (Fang et al., 1969; Lamb et al., 1995). It has been found in many proteins from bacteria to humans, and is involved in many processes such as cell cycle control, transcriptional repression and protein kinase inhibition (Goebel and Yanagida, 1991; Lamb et al., 1995). Interacting with the chaperones Hsp70 and Hsp90, TPR co-chaperones [e.g. Hip (Hsp70 interacting protein), Hop (Hsp organizer protein) and FKBP52 (member of the FK-506 binding protein family)] participate in AR function, by facilitating steroid receptor maturation, maintaining the inactive cytoplasmic receptor in a state of high binding affinity to hormones, and assisting in nuclear translocation and degradation of receptors (Fang et al., 1969; Pratt and Toft, 1997; Smith, 2004; Prescott and Coetzee, 2006).

SGTA, which interacts with Hsp70 and Hsp90 (Liu et al., 1999; Liu and Wang, 2005), has recently been shown to be a key participant in AR function. SGTA binds to the hinge region of the AR (Buchanan et al., 2007). Knockdown of SGTA resulted in increased AR activity and promiscuous activation of the AR by non-classical ligands (e.g. progesterone),
whereas SGTA over-expression inhibited AR activity in response to dihydrotestosterone (Buchanan et al., 2007). SGTA was shown to restrain AR function by promoting AR localization in the cytoplasm (Buchanan et al., 2007). Although these experiments were performed in cultured cell lines, we assume they provide compelling evidence that SGTA modulates sensitivity in human female physiology.

SGTA may affect PCOS risk via a role in apoptosis, as well as androgen signaling. Over-expression and knockdown experiments suggested that SGTA promotes apoptosis by enhancing DNA fragmentation and nuclear breakdown (Wang et al., 2005; Yin et al., 2006). Another group found that SGTA knockdown led to apoptosis via misaligned chromosomes and mitotic arrest (Winnefeld et al., 2006). Recent work comparing gene expression profiles in ovarian tissue from women with and without PCOS has implicated apoptosis as a possible pathway contributing to PCOS (Jansen et al., 2004; Hughes et al., 2006; Wood et al., 2007). Genes for Hsp70 and Hsp90, which participate in apoptosis and are known binding partners of SGTA, also exhibited reduced expression in PCOS ovaries (Jansen et al., 2004; Arya et al., 2007). Clearly further work is needed to define the molecular role of SGTA in androgen signaling and apoptosis in PCOS. Given that PCOS is a syndrome with multiple features, SGTA is an ideal candidate given that it may influence multiple processes.

Our results suggest yet another pathway which may be affected by SGTA, that of insulin signaling. In our data, variation in the SGTA gene was related to insulin resistance, and consequently increased insulin secretion in PCOS. This is a novel finding, and suggests SGTA may be a connection between hormone action and metabolic signaling pathways in the pathogenesis of PCOS.

Our results provide preliminary evidence that SGTA genetic variants may be associated with PCOS risk. Because the three studied SNPs do not change the SGTA amino acid sequence, their functional significance remains to be determined in future study. They may affect splicing of the SGTA transcript or expression of SGTA and/or other genes, or may be in LD with SGTA coding variants yet to be discovered. Because one SNP in these haplotypes is located in the 3’ untranslated region, an effect on transcript stability or translational efficiency is possible (Mazumder et al., 2003). Considering the limits of linkage/association approaches, the association of SGTA with PCOS should be subject to replication efforts in larger sample sizes and independent cohorts (Escobar-Morreale et al., 2005).

In conclusion, the current genetic study of SGTA provides preliminary data implicating SGTA as a genetic determinant of PCOS. SGTA is a potentially exciting candidate for the multi-faceted syndrome of PCOS, because it may play roles in multiple pathways that contribute to the whole picture of PCOS, including androgen action, the insulin axis and apoptosis.

### Supplementary Data

### Funding
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### References

### Table IV. SGTA haplotypes and haplotype frequencies.

<table>
<thead>
<tr>
<th>Haplotype</th>
<th>Overall frequency</th>
<th>PCOS frequency</th>
<th>PCOS count*</th>
<th>Control frequency</th>
<th>Control count</th>
</tr>
</thead>
<tbody>
<tr>
<td>G–A–T</td>
<td>0.761</td>
<td>0.790</td>
<td>437</td>
<td>0.715</td>
<td>246</td>
</tr>
<tr>
<td>A–G–C</td>
<td>0.115</td>
<td>0.102</td>
<td>57</td>
<td>0.135</td>
<td>46</td>
</tr>
<tr>
<td>A–A–C</td>
<td>0.079</td>
<td>0.066</td>
<td>36</td>
<td>0.101</td>
<td>35</td>
</tr>
<tr>
<td>G–G–T</td>
<td>0.031</td>
<td>0.028</td>
<td>16</td>
<td>0.035</td>
<td>12</td>
</tr>
</tbody>
</table>

Order of SNPs in SGTA haplotypes is rs2238614, rs741103 and rs1640262.

*Count represents number of chromosomes assigned a particular haplotype by the expectation maximization algorithm.

PCOS, polycystic ovary syndrome.
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