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# Verification of *ZBTB16* Variant in Polycystic Ovary Syndrome Patients

**Jie Yang**[a,b,c,d,#], **Rusong Zhao**[a,b,c,d,#], **Lei Li**[e], **Guangyu Li**[a,b,c], **Ping Yang**[a,b,c], **Jinlong Ma**[a,b,c,d], **Shigang Zhao**[a,b,c,d], **Han Zhao**[a,b,c,d]

[a]Center for Reproductive Medicine, Cheeloo College of Medicine, Shandong University, Jinan, Shandong, 250012, China

[b]National Research Center for Assisted Reproductive Technology and Reproductive Genetics, Shandong University, Jinan, Shandong, 250012, China

[c]Key Laboratory of Reproductive Endocrinology of Ministry of Education, Shandong University, Jinan, Shandong, 250012, China

[d]Shandong Provincial Clinical Medicine Research Center for Reproductive Health, Shandong University, Jinan, Shandong, 250012, China

[e]Department of Biological Sciences, University of Notre Dame, Notre Dame, IN, USA

## Abstract

**Research Question:** A recent meta-analysis of genome-wide association study (GWAS) has identified that SNP rs1784692 in gene *ZBTB16* is associated with polycystic ovary syndrome (PCOS) in the European population. In this study, we investigated whether rs1784692 is a risk factor for PCOS in Han Chinese women.

**Design:** A case-control study was conducted for Han Chinese women, comprising 526 PCOS patients and 522 control subjects. TaqMan-MGB probe assay was used for variant rs1784692's genotyping. Dominant model and additive model were employed for genotype-phenotype correlation analysis in PCOS and control samples.

**Results:** Minor allele C of rs1784692 is associated with PCOS (OR = 0.556, 95%CI 0.408-0.759, $P = 1.83\times10^{-4}$), even after body mass index (BMI) and age adjustment ($OR_{adj}$ = 0.539, 95%CI 0.391-0.743, $P_{adj} = 1.62\times10^{-4}$). Genotype-phenotype analysis of dominant model showed that the mean level of BMI in the CC+CT group was higher than the TT group in PCOS cases (27.12 ± 5.82 vs. 24.57 ± 4.52, $P = 1.0\times10^{-3}$), but not in control groups, indicating that

Addresses, telephones and e-mails of corresponding authors: **Shigang Zhao**, National Research Center for Assisted Reproductive Technology and Reproductive Genetics, No. 44, Wenhua Xi Road, Jinan 250001, People's Republic of China (Telephone: +86-18817822027, zsg0108@126.com).; **Han Zhao,** National Research Center for Assisted Reproductive Technology and Reproductive Genetics, No. 44, Wenhua Xi Road, Jinan 250001, People's Republic of China (Telephone: +86-18668952989, hanzh80@yahoo.com.

[#]These authors contributed equally to this work.



**Conflict of interest:** The authors declare that they have no conflict of interest.

minor allele C of rs1784692 associates with BMI level in PCOS cases. Moreover, the mean level of luteinizing hormone (LH) in CC+CT group was lower than the TT group both in PCOS and control subjects (9.33 ± 5.08 vs. 10.93 ± 5.91, $P = 0.036$; 4.39 ± 1.66 vs. 4.89 ± 2.07, $P = 0.021$). Genotype-phenotype analysis of additive model showed that the mean level of BMI in TC group was higher than the TT group in PCOS patients when compared with the control subjects (27.14 ± 5.81 vs. 24.57 ± 4.52, $P = 3.06\times10^{-3}$).

**Conclusions:** The SNP rs1784692 in gene *ZBTB16* is associated with PCOS and BMI level in Han Chinese women.

## Introduction

PCOS is a disorder that features ovulatory dysfunction, polycystic ovarian morphology and hyperandrogenism that affects 5.6% Chinese women based on 2003 Rotterdam criterion (McCartney et al., 2016; Norman et al., 2007). The syndrome is also associated with persistently rapid gonadotropin-releasing hormone pulses, an excess of luteinizing hormone, and insufficient follicle-stimulating hormone (FSH) secretion, which contribute to excessive ovarian androgen production and ovulatory dysfunction (McCartney et al., 2016). Previous genetic studies among populations of PCOS patients included molecular genetic studies, familial studies, twin studies, and GWAS (Mykhalchenko et al., 2017). A Dutch twin-family study demonstrated a large influence of genetic factors on the pathogenesis of PCOS, justifying the search for susceptibility genes (Vink et al., 2006). Currently, 11 loci for PCOS have been identified in Han Chinese women by GWAS, which related to the genomic regions of *THADA*, *LHCGR*, *DENND1A*, *FSHR*, *C9orf3*, *RAB5B*, *YAP1*, *HMGA2*, *TOX3*, *INSR* and *SUMO1P1* (Chen et al., 2011; Shi et al., 2012). Previous GWAS studies in European ancestry women based on guidelines of National Institutes of Health (NIH) identified three loci that reached genome-wide significance for PCOS, *GATA/NEIL2, FSHB/ARL14EP,* and *C9orf3/FANCC* locus (Hayes et al., 2015). Day et al. (2015) found six signals from self-reported PCOS in/near genes *ERBB4/HER4, YAP1, THADA, FSHB, RAD50* and *KRR1* in cases of White European ancestry (Day et al., 2015).

Recently, an international meta-analysis of GWAS has identified three novel loci are (near *PLGRKT, ZBTB16* and *MAPRE1*) associated with PCOS (Day et al., 2018). However, whether the three novel loci associated with PCOS in the Chinese population remains unknown.

The aim of this study was to investigate whether the three new loci identified in PCOS cases from women with European ancestry are associated with PCOS in Han Chinese population. The SNP rs1784692 in gene *ZBTB16* reached nominal significance ($P < 0.05$), though not achieving genome-wide significance ($P < 5\times10^{-8}$) in GWAS data from Han Chinese population (Supplemental table S1) from the Center for Reproductive Medicine, Cheeloo College of Medicine, Shandong University, whereas the other two SNPs (rs10739076 and rs853854, near *PLGRKT* and *MAPRE1*, respectively) did not reach nominal significance ($P < 0.05$). Meta-analysis for the combined samples (all samples in this study, GWAS1 and GWAS2) was performed by the fixed effects meta-analysis implemented in PLINK

(Supplemental table S2). Therefore, we chose rs1784692 to perform case-control study. We also evaluated the influence of genetic variation on the endocrine and metabolic features.

## Materials and Methods

### Subjects

The cohort consisted of 526 PCOS patients and 522 control subjects, all of which were Han Chinese women. Samples were recruited from the Center for Reproductive Medicine, Cheeloo College of Medicine, Shandong University. Cases diagnosed with PCOS conform to the Rotterdam criteria when at least two of the following three criteria were met: oligo- and/or anovulation, clinical and/or biochemical signs of hyperandrogenism (HA), and polycystic ovaries (PCO) based on ultrasound findings (either ≥ 12 follicles with a diameter of 2–9 mm in at least one ovary or increased ovarian volume >10 ml). Clinical HA was assessed using Ferriman-Gallwey score ≥ 6. Biochemical HA was defined by elevated total serum concentration of testosterone (T) ≥ 60 ng/dL. Diseases which have similar clinical manifestations, such as congenital adrenal hyperplasia, androgen-secreting tumours, and Cushing's syndrome, were excluded (Rotterdam EA-SPcwg, 2004). Women in the control group had normal menstrual cycles without HA or PCO. Individuals who were under medications affecting hormones or influencing endocrine diseases were excluded. Written informed consents were obtained from all participants.

### SNP genotyping

SNP rs1784692 in *ZBTB16* gene was selected for further study. Genomic DNA from peripheral whole blood was extracted with QIAamp DNA mini kit (QIAGEN, Hilden, Germany). TaqMan-MGB probe assay (Thermo Fisher Scientific, Waltham, USA, Assay ID: C__8909529_10, Catalogue: 4351379) was used for genotyping. Amplification reactions were carried out on 384-well plates with LightCycler® 480. No samples failed genotyping in this study. Seven samples of genomic DNA from peripheral whole blood were chosen randomly from the PCOS patients and the control subjects for quality controls. Taqman-MGB probe assay was used for genotyping the fourteen samples. This genotyping was repeated three times. No sample failed genotyping among the fourteen samples and the concordance rate reached 100%.

### Clinical and biochemical measurements

All samples underwent standardized clinical and biochemical measurements. The BMI was calculated on the basis of weight and height ($kg/m^2$) when the subjects were recruited. Levels of hormones in serum such as total T, LH and FSH were measured from fasting blood samples at day 2–4 of menstrual cycle. While for women with menstrual irregularities, the fasting blood samples were obtained when there were no dominant follicles in the ultrasound images. Chemiluminescence immunoassay was used to measure the levels of hormones using the Roche Cobas e 601.

### Statistical analysis

The independent samples *t*-test was applied to analyse continuous variables of clinical data which are presented as mean ± SD. The comparison of allele frequencies between

PCOS patients and control subjects were analysed by chi-square test. Genetic models were divided into additive model (+/+ vs. +/− vs. −/−), dominant model (+/+ plus +/− vs. −/−) and recessive model (+/+ vs. +/− plus A Bonferroni approach was used for genotype frequencies in the additive model. Dominant model and additive model were selected for genotype-phenotype analysis according to the *P* value of the genotype frequencies ($P_{dom}$ = $1.0\times10^{-3}$, $P_{add}$ = $1.0\times10^{-3}$). One-way ANOVA, Bonferroni approach and Dunnett's T3 were used for genotype-phenotype analysis of additive model. The Hardy-Weinberg equilibrium calculation was conducted by Stata 13.1 software. These analyses were carried out by SPSS version 23.0 (SPSS Inc., Chicago, IL, USA).

## Results

### Basic clinical features

Clinical characteristics of 526 PCOS patients and 522 control subjects are shown in Table 1. After adjustment for age, PCOS patients had a higher BMI than control subjects [24.90 ± 4.78 vs. 22.95 ± 3.20, $P = 2.66\times10^{-14}$], a higher LH level [10.73 ± 5.83 vs. 4.79 ± 2.00, $P = 4.28\times10^{-81}$], and a higher T level [46.25 ± 16.48 vs. 26.70 ± 11.93, $P = 3.50\times10^{-87}$].

### SNP rs1784692 is associated with PCOS in Han Chinese women

Allele frequencies and genotype frequencies for rs1784692 are shown in Table 2. Minor allele C of rs1784692 in gene *ZBTB16* is associated with PCOS with odds ratio (OR) of 0.556 (95% CI 0.408-0.759, $P = 1.83\times10^{-4}$, Table 2), even after BMI and age adjustment ($OR_{adj}$ = 0.539, 95% CI 0.391-0.743, $P_{adj} = 1.62\times10^{-4}$, Table 2). A Bonferroni approach was used in genotype frequency of additive model. It shows that there are statistical differences between- the TT group and TC group, and- TT group and CC group.

### SNP rs1784692 is associated with BMI level in PCOS cases

The dominant model and additive model are more effective than the recessive model for genotype-phenotype analysis, according to the *P* value of genotype frequencies ($P_{dom}$ = $1.0\times10^{-3}$, $P_{add}$ = $1.0\times10^{-3}$, $P_{rec} = 1.9\times10^{-2}$). Therefore, dominant model and additive model were employed for the genotype-phenotype analysis. In dominant model, the TT group can be compared with the TC+CC group in PCOS patients and control subjects. The genotype-phenotype analysis of dominant model showed that the mean level of BMI in CC+CT group was notably higher than TT group in PCOS patients (27.12 ± 5.82 vs. 24.57 ± 4.52, $P = 1.0\times10^{-3}$, Table 3), while the mean level of BMI had no difference between CC+CT subgroup and TT subgroup in the control group (22.93 ± 3.32 vs. 22.96 ± 3.18, $P$ = 0.918, Table 3), thus indicating that minor allele C of rs1784692 associates with BMI level in PCOS cases. Moreover, the mean level of LH in CC+CT group was lower as compared to TT group both in PCOS patients and control subjects (9.33 ± 5.08 vs. 10.93 ± 5.91, $P$ = 0.036; 4.39 ± 1.66 vs. 4.89 ± 2.07, $P$ = 0.021, Table 3). The genotype-phenotype analysis of additive model is presented in Table 4. The mean level of BMI in TC group was higher than TT group in PCOS patients compared with the control group (27.14 ± 5.81 vs. 24.57 ± 4.52, $P = 3.06\times10^{-3}$, Table 4).

## Discussion

In this study, we show that rs1784692 in gene *ZBTB16* associated with PCOS in the Han Chinese population. Previous work on the meta-analysis in women of European ancestry, researchers regarded T allele as rs1784692's effect allele with Odds Ratio 1.15 (95% CI 1.10 ± 1.20, $P = 1.88\times10^{-10}$) (Day et al, 2019). The genotype-phenotype analysis of dominant model provided evidence that the TT group for rs1784692 in gene *ZBTB16* was shown to be associated with lower BMI level in PCOS patients.

The mechanisms and pathophysiology of PCOS are complex because of close connection between variation in aetiologies and the different features (Azziz et al., 2016). The phenotype differs considerably based on ethnicity, life stage, genotype, and environmental factors including lifestyle and bodyweight (Teede et al., 2010).

Obesity is commonly associated with PCOS. In most of the cohorts, such as UK (London/Oxford), Chicago and Boston, BMI in PCOS patients were higher than BMI in control subjects (Day et al., 2018). In addition, this result can be further proved by other cohorts from Cedars-Sinai Medical Center, Massachusetts General Hospital and University of Alabama at Birmingham (Hayes et al, 2015), Northern Han Chinese and southern and central Han Chinese (Chen et al, 2011) in previous GWAS of PCOS. Preceding research also demonstrated women with PCOS had a greater risk of obesity and being overweight (Lim et al., 2012). In European PCOS GWAS meta-analysis, mendelian randomization analyses suggested variants associated with BMI play a causal role in PCOS. In our study, the higher minor allele frequency of rs1784692 in gene *ZBTB16* was shown to be associated with higher BMI level in PCOS. It alludes that *ZBTB16* might play an important role in the aetiology of PCOS through influencing BMI.

*ZBTB*16 (Zinc Finger and BTB Domain Containing 16), also known as *ZNF145* and *PLZF*, was initially discovered in human as a cause of retinoic acid-resistant acute promyelocytic leukaemia in the form of fusion protein PLZF-RARα associated with the t (11; 17) (q23; q21) translocation (Grignani et al., 1998). The gene database from NCBI shows that the *ZBTB16* gene is a member of the Krueppel C2H2-type zinc-finger protein family and encodes a zinc finger transcription factor that contains nine Kruppel-type zinc finger domains at the carboxyl terminus. This nuclear protein is involved in cell cycle progression, and interacts with a histone deacetylase. The *ZBTB16* gene broadly expresses in fat (RPKM 27.9), ovary (RPKM 22.2) and 19 other tissues (Supplemental Figure 1). Indeed, *ZBTB16* is upregulated in vitro during adipocyte differentiation and involved in the control of early stages of spermatogenesis (Ambele et al., 2016; Lovelace et al., 2016). In addition, *ZBTB 16* overexpression can promote white adipogenesis and induce brown-like adipocyte formation for bovine white intramuscular preadipocytes (Wei et al., 2018).

The TT group for rs1784692 in gene *ZBTB16* was shown to be associated with higher LH levels in both PCOS patients and control subjects. Furthermore, *ZBTB16* has been proven as an androgen-responsive gene with anti-proliferative activity in prostate cancer cells and act on emergency or stress haematopoiesis (Jiang et al., 2004; Dick et al., 2009).

In conclusion, we confirmed for the first time that rs1784692 is associated with PCOS in Han Chinese population and its higher minor allele frequency is related to higher BMI levels in PCOS. Thus, *ZBTB16* might play an important role in the aetiology of PCOS through influencing BMI.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

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## Biography

Jie Yang is studying at the center for reproductive medicine of Shandong University, majoring in obstetrics and gynecology, specializing in reproductive medicine. Her research focus on reproductive endocrinology and polycystic ovary syndrome.

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**Key message**

Rs1784692 in gene *ZBTB16* has been identified associated with polycystic ovary syndrome (PCOS) in European ancestry. A case-control study was conducted including 526 PCOS patients and 522 control subjects of Han Chinese women. We concluded that rs1784692 is associated with PCOS and body mass index (BMI) level in Han Chinese.

**Table 1.**

Clinical characteristics of PCOS patients and control subjects

| | PCOS | Controls | *P* |
|---|---|---|---|
| N | 526 | 522 | |
| Age[a](years) | 29.98 ± 3.96 | 31.40 ± 5.06 | $5.24\times10^{-7}$ |
| BMI[a]($kg/m^2$) | 24.90 ± 4.78 | 22.95 ± 3.20 | $2.66\times10^{-14}$ |
| FSH[a](IU/L) | 6.10 ± 1.57 | 7.56 ± 2.85 | $2.58\times10^{-23}$ |
| LH[a](IU/L) | 10.73 ± 5.83 | 4.79 ± 2.00 | $4.28\times10^{-81}$ |
| T[a](ng/dl) | 46.25 ± 16.48 | 26.70 ± 11.93 | $3.50\times10^{-87}$ |

BMI, body mass index; FSH, follicle stimulating hormone; LH, luteinizing hormone; T, Testosterone;

[a]Data are presented as mean ± SD.

**Table 2.**

Allele frequencies and genotype frequencies analyses in PCOS and control

| SNP | Allele | PCOS | Control | OR | *P* | $P_{adj}$ | $OR_{adj}$ |
|---|---|---|---|---|---|---|---|
| rs1784692 | **C**/T | 0.066 | 0.112 | 0.556 (0.408-0.759) | $1.83\times10^{-4}$ | $1.62\times10^{-4}$ | 0.539 (0.391-0.743) |
| **SNP** | **Genotype** | **PCOS** | **Control** | $P_{add}$ | $P_{dom}$ | $P_{rec}$ | |
| rs1784692 | TT/TC/CC | 459/65/2 | 415/97/10 | $1.0\times10^{-3}$ | $1.0\times10^{-3}$ | $1.9\times10^{-2}$ | |

$P_{adj}$, The *P* value calculated by logistic regression analysis taking age and BMI as covariant; $OR_{adj}$, OR calculated by logistic regression analysis taking age and BMI as covariant. Bold face indicates the effect allele.

$P_{add}$ The *P* value of additive genotype model (TT/TC/CC) in the three groups by chi-square test; $P_{dom}$, The *P* value of dominant genotype model (CC+CT/TT) in the two groups by chi-square test; $P_{rec}$, The *P* value of recessive genotype model (CC/CT+TT) in the two groups by chi-square test.

**Table 3.**

The association between risk allele of rs1784692 and clinical characteristics in cases and controls using a dominant model

| Clinical Characteristics | Subject Type | CC+CT(Ncase=67, Ncontrol=107) | TT(Ncase=459, Ncontrol=415) | *P* |
|---|---|---|---|---|
| Age(years) | cases | 30.28 ± 4.06 | 29.93 ± 3.94 | 0.501 |
| | controls | 31.57 ± 4.99 | 31.35 ± 5.08 | 0.691 |
| BMI($kg/m^2$) | cases | 27.12 ± 5.82 | 24.57 ± 4.52 | $1.0\times10^{-3}$ |
| FSH(IU/L) | cases | 6.12 ± 1.45 | 6.10 ± 1.59 | 0.919 |
| LH(IU/L) | cases | 9.33 ± 5.08 | 10.93 ± 5.91 | 0.036 |
| T(ng/dl) | cases | 45.75 ± 19.03 | 46.32 ± 16.10 | 0.790 |

**Table 4.**

The association between risk allele of rs1784692 and clinical characteristics in cases and controls using an additive model

| Clinical Characteristics | Subject Type | TT (Ncase=459, Ncontrol=415) | TC (Ncase=65, Ncontrol=97) | CC (Ncase=2, Ncontrol=10) | $P_{TT\ and\ TC}$ | $P_{TT\ and\ CC}$ | $P_{TCand\ CC}$ |
|---|---|---|---|---|---|---|---|
| Age(years) | cases | 29.93±3.94 | 30.38±4.06 | 27.00±2.83 | 1.00 | 0.887 | 0.702 |
| | controls | 31.35±5.08 | 31.48±4.91 | 32.40±5.89 | 1.00 | 1.00 | 1.00 |
| BMI(kg/m$^2$) | cases | 24.57±4.52 | 27.14±5.81 | 26.68±8.67 | $3.06\times10^{-3}$ | 0.974 | 1.00 |
| | controls | 22.96±3.18 | 22.73±3.34 | 24.85±2.52 | 1.00 | 0.197 | 0.139 |
| FSH(IU/L) | cases | 6.10±1.59 | 6.15±1.47 | 5.31±0.21 | 1.00 | 1.00 | 1.00 |
| | controls | 7.60±2.97 | 7.41±2.36 | 7.47±1.84 | 1.00 | 1.00 | 1.00 |
| LH(IU/L) | cases | 10.93±5.91 | 9.30±5.14 | 10.44±3.29 | 0.105 | 1.00 | 1.00 |
| | controls | 4.89±2.07 | 4.39±1.71 | 4.42±1.16 | 0.078 | 1.00 | 1.00 |
| T(ng/dl) | cases | 46.32±16.10 | 45.19±18.57 | 64.04±33.67 | 1.00 | 0.389 | 0.335 |
| | controls | 26.88±12.06 | 25.55±11.32 | 30.35±12.45 | 0.964 | 1.00 | 0.677 |