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GENETICS

CYP1A1 and CYP1B1 genetic polymorphisms and uterine leiomyoma risk in Chinese women

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Abstract

Purpose The aim of the study was to evaluate the association of CYP1A1 and CYP1B1 polymorphisms with uterine leiomyoma in Chinese women.

Methods We investigated 100 women with clinically diagnosed uterine leiomyoma and 110 healthy normal subjects from Chinese women. The genetic distribution of two CYP1A1 polymorphisms at MspI, Ile462Val and four CYP1B1 polymorphisms at Arg48Gly, Ala119Ser, Leu432Val, Asp449Asp were analyzed by polymerase chain reaction–restriction fragment length polymorphism and DNA sequencing method.

Results All the SNPs showed polymorphisms in Chinese women. The genotype A/G and the allele G on Ile462Val was significantly different between uterine leiomyoma patients and controls ($P<0.05$).

Conclusion These results suggest that the genotype of CYP1A1 Ile462Val was associated with the increased risk of uterine leiomyomas in Chinese women.

Keywords CYP1A1 · CYP1B1 · Uterine leiomyoma · Genetic polymorphism

Capsule This is the first report that demonstrates the polymorphism at Ile462Val of CYP1A1 to be associated with uterine leiomyoma in Chinese women.

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Introduction

Uterine leiomyoma is the most common benign smooth muscle cell tumor of the myometrium, occurring in as many as 30% of women over 35 years of age. The majority of patients have multiple leiomyomas, and each leiomyoma is thought to be clonal, arising independently from a single smooth muscle cell [1]. The growth and the development of leiomyoma are estrogen dependent [2–4]. It was found that the majority of muscle cells contributing to leiomyoma express both the estrogen receptors (ER) ERalpha and ERbeta [5]. However, exact mechanisms explaining the occurrence of leiomyoma remain unclear. Several single nucleotide polymorphisms (SNPs) located in Vascular endothelial growth factor (VEGF), catechol-O-methyltransferase (COMT) and the estrogen receptor gene have been studied to elucidate the association with the risk of uterine leiomyoma [6–8].

The P450 cytochrome system (CYP450) is a group of enzymes involved in steroid hormone biosynthesis as well as in metabolic activation of carcinogens [9, 10]. CYP1A1 and CYP1B1 are the main CYP450 enzymes involved in estrogen catabolism. The CYP1A1 gene, located on chromosome 15q22–q24, is 5,987 base pairs long and encodes a 512-amino acid protein. To date, 19 common polymorphisms of this gene have been identified [11]. Polyaromatic hydrocarbons and other chemicals serve as inducers as well as substrate in the regulation of gene expression [12]. The CYP1B1 gene has been mapped to chromosome 2p21–p22. It is similar in size to the CYP1A1 gene (8,546 base pairs in length and encoding a 543-amino acid protein). Currently, approximately 42 common CYP1B1 allele variants have been reported [11]. The substrates of CYP1B1 enzymatic activity are also the inducers of gene transcription, consistent with CYP1A1

activity [12]. The polymorphisms of CYP1A1 and CYP1B1 gene had been studied in relation to the hormonally relevant diseases, such as endometriosis, breast cancer, endometrial adenocarcinoma [13–17].

In this report, we evaluated two CYP1A1 SNPs—MspI, Ile462Val and four CYP1B1 SNPs—Arg48Gly, Ala119Ser, Leu432Val, Asp449Asp and their associations with uterine leiomyoma in a Chinese women population with clinically and surgically diagnosed uterine leiomyoma in comparison to a healthy control population.

Materials and methods

Study population

We recruited 100 women with clinically diagnosed uterine leiomyoma undergoing surgical intervention at the Department of Gynecology of Neijiang First People's Hospital from May 2007 to January 2008. Local institutional review board approval and informed consent from all subjects were obtained. Leiomyoma were diagnosed by detailed sonographic examination and confirmed by histological examination after hysterectomy or myomectomy. Blood was taken from all participants by peripheral antecubital venous puncture and stored at −20°C until analysis. Among the leiomyoma patients, the average age was 46.95±18.05. Population controls were recruited from healthy women. After adjustment, there were no difference of age, parity, age at last birth, cigarette smoking and oral contraceptive use between the case group and control group.

DNA extraction and genotyping

Genomic DNA was isolated from peripheral blood by using a blood DNA isolation kit (Bioteke Inc., China). The genotypes of CYP1A1 gene MspI, Ile462Val and CYP1B1 gene Arg48Gly, Ala119Ser, Leu432Val, Asp449Asp were determined by using a polymerase chain reaction–restriction fragment length polymorphism method (PCR–RFLP), the PCR primers were designed based on the Gen-Bank reference sequence and described previously [18, 19] (see Table 1 for primer sequences and reaction conditions). The 25 μl reaction mix for each PCR product comprised: 25–50 ng of genomic DNA, 25 mM $MgCl_2$, 10× PCR Buffer 3.3 μl, 0.4 pM of each primer, 2.5 mM of each dNTP 3.3 μl, 1 U Taq polymerase (Tiangen) and add DDH_2O to 25 μl reactions. Digestion of 2 μl of each PCR amplification was accomplished with 2 U of the specific endonuclease for 16 h at 37°C following the supplier's directions for buffer conditions. PCR and digestion products were analysed directly by vertical non-denaturing polyacrylamide gel electrophoresis with 1× TBE continuous buffer system and visualized by silver staining. To confirm the genotyping results, One of PCR-amplified DNA from heterozygote samples chosen in each SNP were examined by DNA sequencing, and the results were 100% concordant.

Statistical analysis

Genotype and allele frequencies of CYP1A1 gene and CYP1B1 gene were compared between uterine leiomyoma cases and controls using the χ^2 test and Fisher's exact test when appropriate, and odds rations (OR) and 95% confidence intervals (CIs) were calculated to assess the relative risk conferred by a particular allele and genotype. Hardy–Weinberg equilibrium was tested with a goodness of fit χ^2-test with one degree of freedom to compare the observed genotype frequencies among the subjects with the expected genotype frequencies. Statistical significance was assumed at the $P<0.05$ level. The SPSS statistical software package version 11.5 was used for all of the statistical analysis.

Table 1 Primer sequences and reaction conditions for CYP1A1 and CYP1B1 polymorphisms

Polymorphism	Reference SNP ID	Primer sequences	Annealing temp (°C)	Restriction enzyme	Product size (bp)
CYP1A1 MspI (T/C)	rs4646903	5′-CAGTGAAGAGGTGTAGCCGCT-3′ 5′-TAGGAGTCTTGTCTCATGCCT-3′	58	HhaI	340
CYP1A1 Ile462Val (A/G)	rs1048943	5′-GATCTGAGTTCCTACCTGA-3 5′-TAGCGTCCAAGAGAAAGACCTCCCAGCGCTCAA-3′	55	HincII	147
CYP1B1 Arg48Gly (C/G)	rs10012	5′-GGCAACGGAGGCGGCAGCAC-3′ 5′-GGAAAACGTCGCCGTAGCGCCG-3′	65	BSHTI	135
CYP1B1 Ala119Ser (C/T)	rs1056827	5′-TCGGCCTTCGCCGACCGGCC-3′ 5′-TGCGCGCCGCTGCACCTTCCAG-3′	56	PdiI	108
CYP1B1 Leu432Val (C/G)	rs1056836	5′-CACCACTGCCAACACCTCTGTC-3′ 5′-AGTTCTCCGGGTTAGGCCACTTAA-3′	55	BSPTI	113
CYP1B1 Asp449Asp (T/C)	rs1056837	5′-CCAGCTCGATTCTTGGACAAGGA-3′ 5′-CTGGTGAGCCAGGATGGAGATG-3′	60	FokI	147

Table 2 The genotype frequencies of two polymorphisms of CYP1A1 gene between Chinese uterine leiomyoma patients and controls

SNP	Genotype	Cases n=100 (%)	Control n=110 (%)	Adjusted OR (95% CI)	P-value
MspI	TT	34 (34.0)	43 (39.1)	1.00 (Ref.)	–
	TC	48 (48.0)	50 (45.5)	1.21 (0.67–2.21)	0.526
	CC	18 (18.0)	17 (15.4)	1.34 (0.60–2.98)	0.474
	TC+CC	66 (66.0)	67 (60.9)	1.25 (0.71–2.19)	0.445
Ile462Val	AA	56 (56.0)	82 (74.6)	1.00 (Ref.)	–
	AG	41 (41.0)	27 (24.5)	2.22 (1.23–4.02)	0.008
	GG	3 (3.0)	1 (0.9)	4.39 (0.45–43.32)	0.168
	AG+GG	44 (44.0)	28 (25.5)	2.30 (1.28–4.12)	0.005

OR Odds ratio, *95% CI* 95% confidence interval, *Ref.* reference category

Results

The genotype and allele frequencies of CYP1A1

The genotype and allele frequencies of CYP1A1 gene MspI, Ile462Val in the group of patients with uterine leiomyoma and in the control group were shown in Tables 2 and 3. The genotype distributions of two polymorphisms among the controls and the cases were in Hardy–Weinberg equilibrium.

There was no significant difference in the genotype and allele frequencies of the CYP1A1 MspI. However, the genotype on Ile462Val was observed to be significantly different between uterine leiomyoma patients and controls. There were 41% of patients with leiomyoma who had genotype A/G versus 24.5% of healthy controls (P=0.008; Table 2). The allele frequencies for Ile462Val were also different (P=0.006; Table 3) with OR and 95% CI of 2.02 and 1.22–3.37, respectively.

The genotype and allele frequencies of CYP1B1

The genotype and allele frequencies of CYP1B1 gene Arg48Gly, Ala119Ser, Leu432Val, Asp449Asp in the group of patients with uterine leiomyoma and in the control group were shown in Tables 4 and 5. The genotype distributions of four polymorphisms among the controls and the cases were in Hardy–Weinberg equilibrium. There were no significant differences in the genotype and allele frequencies of the CYP1B1 gene Arg48Gly, Ala119Ser, Leu432Val and Asp449Asp polymorphisms between the two groups.

Discussion

Uterine leiomyoma is a complicated disease related to an interaction between multiple genes, hormone, growth factor, cytokines, and the environment. Steroid hormones secreted by the ovaries are essential for the growth of leiomyoma [20]. Both the estrogen receptors ERalpha and ERbeta were found in most of muscle cells contributing to leiomyoma expression [5]. Yager and Liehr [21] found predominant 4-hydroxylase activities in human uterine myometrium and benign uterine leiomyomas. In addition, hydroxyestrogens were shown to induce endometrial adenocarcinoma in mice [22]. These reports strongly suggest that estrogens and its metabolic product have effects on the occurrence and development of uterine leiomyoma. Since CYP1A1 and CYP1B1 polymorphisms are expected to affect the synthesis or degradation of estrogens, we speculate that the CYP1A1 gene and CYP1B1 gene play important roles in the development and progression of uterine leiomyomas.

CYP1A1 plays a central role in the 2-hydroxylation of estradiol and estrone to 2-hydroxy catechol metabolites for subsequent O-methylation to 2-methoxy intermediates [23]. While the 2-hydroxylation products (2-OH estradiol catechol and 2-OH estrone catechol) are devoid of estrogenic

Table 3 The allele frequencies of two polymorphisms of CYP1A1 gene between Chinese uterine leiomyoma patients and controls

SNP	Allele	Cases n=200 (%)	Control n=220 (%)	Adjusted OR (95% CI)	P-value
MspI	T	116 (58.0)	136 (61.8)	1.00 (Ref.)	
	C	84 (42.0)	84 (38.2)	1.17 (0.79–1.73)	0.425
Ile462Val	A	153 (76.5)	191 (86.8)	1.00 (Ref.)	
	G	47 (23.5)	29 (13.1)	2.02 (1.22–3.37)	0.006

OR Odds ratio, *95% CI* 95% confidence interval, *Ref.* reference category

Table 4 The genotype frequencies of four polymorphisms of CYP1B1 gene between Chinese uterine leiomyoma patients and controls

SNP	Genotype	Cases n=100 (%)	Control n=110 (%)	Adjusted OR (95% CI)	P-value
Arg48Gly	CC	70 (70.0)	71 (64.5)	1.00 (Ref.)	–
	CG	29 (29.0)	39 (35.5)	1.33 (0.74–2.38)	0.342
	GG	1 (1.0)	0 (0.0)	0.50 (0.42–0.59)	0.316
	CG+GG	30 (30.0)	39 (35.5)	1.28 (0.72–2.29)	0.401
Ala119Ser	GG	57 (57.0)	63 (57.3)	1.00 (Ref.)	–
	GT	40 (40.0)	45 (40.9)	1.02 (0.58–1.78)	0.950
	TT	3 (3.0)	2 (1.8)	0.60 (0.10–3.74)	0.584
	GT+TT	43 (43.0)	47 (42.7)	0.99 (0.57–1.71)	0.968
Leu432Val	CC	71 (71.0)	70 (63.6)	1.00 (Ref.)	–
	CG	29 (29.0)	40 (36.4)	1.40 (0.78–2.50)	0.257
Asp449Asp	CC	76 (76.0)	71 (64.5)	1.00 (Ref.)	–
	CT	23 (23.0)	38 (34.5)	1.77 (0.96–3.26)	0.066
	TT	1 (1.0)	1 (1.0)	1.07 (0.07–17.44)	0.962
	CT+TT	24 (24.0)	39 (35.5)	1.74 (0.95–3.18)	0.070

OR Odds ratio, *95% CI* 95% confidence interval, *Ref.* reference category

activities and the 2-methoxy derivatives shown to possess anti-proliferative and anti-angiogenic properties [24–26], another mutually exclusive pathway of 16α-hydroxylation leads to metabolites with strong estrogenic properties and were linked to estrogen-induced carcinogenesis in both laboratory animals and humans [27, 28]. It is possible that a certain genetic polymorphism affecting the CYP1A1 enzyme activity might induce the uterine leiomyomas.

We found that the CYP1A1 Ile462Val was significantly different between uterine leiomyoma patients and controls. The heterozygous A/G genotype and the allele G were found more often among the patients with uterine leiomyomas. Our data indicated that the genotype of CYP1A1 Ile462Val was associated with the increased risk of uterine leiomyomas in Chinese women. However, there was non-significant association in T/C polymorphism of the CYP1A1 MspI between two groups.

The result of the present study corresponded well with those of other studies on the CYP1A1 polymorphism and the risk of estrogen-dependent diseases. Herr et al. [29] reported the C allele of CYP1A1 Thr461Asn had a statistical significant association with the occurrence of uterine leiomyoma in Germany (P=0.025, OR=2.68). Boyapati et al. [30] found the homozygosity for MspI and Ile462Val alleles were significantly associated with breast cancer risk, particularly in postmenopausal women with a long duration of estrogen exposure in Chinese population. Arvanitis et al. [13] reported the variant genotype T/T of the CYP1A1 MspI exhibited a protective effect, with a 38% reduction in the odds for endometriosis development (OR= 0.62; 95% CI=0.440–0.883). Esinler et al. [31] reported that the rate of the CYP1A1 Ile462Val A/G genotype was significantly higher in patients with PCOS than in the controls (OR=7.8, 95% CI=3.45–17.52). We concluded that the CYP1A1 gene played an important role in the development and progression of estrogen-dependent diseases.

CYP1B1 is a phase I enzyme that catalyzes the conversion of 17b-estradiol (E2) to the catechol estrogens, 4-hydroxyestradiol (4-OH-E2) and 2-hydroxyestradiol (2-OH-E2) and is involved in the activation of polycyclic aromatic hydrocarbons [32]. Metabolic activation of 4-hydroxy-estrogens induces DNA damage by hydroxylation

Table 5 The allele frequencies of four polymorphisms of CYP1B1 gene between Chinese uterine leiomyoma patients and controls

SNP	Allele	Cases n=200 (%)	Control n=220 (%)	Adjusted OR (95% CI)	P-value
Arg48Gly	C	169 (84.5)	181 (82.3)	1.00 (Ref.)	–
	G	31 (15.5)	39 (17.7)	0.85 (0.51–1.43)	0.541
Ala119Ser	G	154 (77.0)	171 (77.7)	1.00 (Ref.)	–
	T	46 (23.0)	49 (22.3)	1.04 (0.66–1.65)	0.859
Leu432Val	C	171 (85.5)	180 (81.8)	1.00 (Ref.)	–
	G	29 (14.5)	40 (18.2)	0.76 (0.45–1.29)	0.309
Asp449Asp	C	175 (87.5)	180 (81.8)	1.00 (Ref.)	–
	T	25 (12.5)	40 (18.2)	0.64 (0.37–1.11)	0.108

OR Odds ratio, *95% CI* 95% confidence interval, *Ref.* reference category

of guanine bases in DNA [33]. Several additional evidences suggest that oxidation of 4-hydroxy estrogens is the pathway leading to estrogen-induced cancer, such as endometrial cancer [22]. Therefore, these products may increase risk for uterine leiomyomas, which is though to be estrogen dependent and the monoclonal neoplasm [1, 20].

However, in our study we found that there is no association between uterine leiomyoma and the genetic polymorphisms of CYP1B1 Arg48Gly, Ala119Ser, Leu432Val and Asp449Asp. Only borderline significance was observed at the allele Asp449Asp (P=0.064).

Many reports were published on CYP1B1 gene for a variety of estrogen dependent diseases and showed the inconsistency result. Several epidemiological studies demonstrated no association between the CYP1B1 polymorphism and breast cancer in Asia and Caucasian population [34, 35]. And a recent case-control study in Korea showed that the risk of endometriosis was not significantly increased in carriers of CYP1B1 gene Arg48Gly, Ala119Ser, Leu432Val and Asp449Asp alleles [36]. However, Hsieh et al. [20] found a significant association of the Val432Leu polymorphism with an increased risk of breast cancer (OR= 2.3, 95% CI=1.2–4.5). Through the meta-analysis, Paracchini et al. [35] found a significant effect of age on the association between CYP1B1 Val432Leu and breast cancer in Caucasians. The risk of breast cancer seemed to be higher for the central age classes (45–59 years), while it was lower in either older or younger women. Sillanpää et al. [37] reported a significant increase in the breast cancer risk was seen for women who had smoked one–nine cigarettes/day and carried the CYP1B1 432Val allele. It was conjectured that the contribution of CYP1B1 polymorphism to uterine leiomyoma risk might vary from one population to another on account of differences in the prevalence of various polymorphisms across populations. And the development of estrogen-induced diseases was caused by interaction between gene and environment factors.

In summary, to our knowledge, this is the first report which explored the polymorphisms of CYP1A1 gene MspI, Ile462Val, and CYP1B1 gene Arg48Gly, Ala119Ser, Leu432Val, Asp449Asp in uterine leiomyoma. Interestingly, codon Ile462Val is the only polymorphism that was observed to be a risk factor for uterine leiomyoma. These results suggest that genetic polymorphisms of Ile462Val might be clinically important in the development and progression of uterine leiomyomas. Though this study has been carried out with a small sample size, further studies are in progress with a larger sample size to investigate the role of gene–environment interactions in the development of uterine leiomyoma.

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