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# Passive smoking, Cyp1A1 gene polymorphism and dysmenorrhea

**Hong Liu**[1], **Fan Yang**[2], **Zhiping Li**[2], **Changzhong Chen**[3], **Zhian Fang**[3], **Lihua Wang**[1], **Yonghua Hu**[1,*], and **Dafang Chen**[1,*]

[1]Department of Epidemiology and Biostatistics, School of Public Health, Peking University Health Science Center, Beijing, China

[2]Anhui Biomedical institute, Anhui Province, China

[3]Brigham and Women's hospital, Harvard Medical School, Boston, Massachusetts, USA

## Abstract

**Objective—**This study investigated whether the association between passive smoking exposure and dysmenorrhea is modified by two susceptibility genes, CYP1A1MspI and CYP1A1HincII.

**Methods—**This report includes 1645 (1124 no dysmenorrhea, 521 dysmenorrhea) nonsmoking and nondrinking newly wed female workers at Anqing, China between June 1997 and June 2000. Multiple logistic regression models were used to estimate the associations of passive smoking exposure and genetic susceptibility with dysmenorrhea, adjusting for perceived stress.

**Results—**When stratified by women genotype, the adjusted OR of dysmenorrhea was 1.6 (95%CI=1.3-2.1) for passive smoking group with Ile/Ile462 genotype, and 1.5 (95%CI=1.1-2.1) with C/C6235 genotype, compared to non passive smoking group, respectively. The data further showed that there was a significant combined effect between passive smoking and the CYP1A1 Msp1 C/C6235 and HincII Ile/Ile462 genotype (OR=2.6, 95%CI=1.3-5.2).

**Conclusion—**CYP1A1 MspI and HincII genotypes modified the association between passive smoking and dysmenorrhea.

### Keywords

Cytochrome P-450 CYP1A1; dysmenorrhea; polymorphism; genetic; tobacco smoke polution

## Introduction

Dysmenorrhea is a common gynecologic disorder in women of reproductive age. Dysmenorrhea is categorized as primary (in the absence of organic pelvic lesions) and as secondary (in the presence of organic diseases such as endometriosis, adhesive disease, and uterine pathology). Reported prevalence ranges from 47 to 72% for various age groups(1-3). This condition accounts for significant school absenteeism, lost working time, and reduced quality of life(4-6). In the United States it is estimated that about 600 million working hours

* Correspondence author, Correspondence and requests for reprints should be addressed to: Department of Epidemiology and Biostatistics, Peking University Health Science Center, 38 Xueyuan Road, Haidian District, Beijing, 100083, Tel (86) 10-8280-1189 Fax (86) 10-8280-1189, Email: dafangchen@bjmu.edu.cn; yhhu@bjmu.edu.cn.

are lost annually as a result of primary dysmenorrhea(4), and it is now recognized as an important women's health issue(7).

A growing body of evidence demonstrates an association between environmental and occupational exposures and adverse reproductive outcomes. Although limited data are available for dysmenorrhea, epidemiological studies have shown a link between dysmenorrhea and several environmental risk factors, including current cigarette smoking(8-11), body mass index(12), and contraceptive use(13). However, not all individuals who are exposed to these environmental/occupational chemicals have adverse reproductive outcomes, the reason for this variability was largely unknown, but may be related to genetic susceptibility. Tobacco smoke contains approximately 4000 compounds(14). The most important carcinogens in tobacco smoke are polycyclic aromatic hydrocarbons (PAHs), arylmines, and N-nitrosamines(15).

The ability of an individual to convert toxic metabolites of cigarette smoke to less harmful moieties is critical for minimizing the adverse health effects of these compounds. For example, the detoxification of PAHs in humans involves two parts: phase I, in which the inhaled hydrophobic PAHs are converted mainly though aryl hydrocarbon hydroxylase activity into hydrophilic, and phase II, in which reactive hydrophilic intermediates such as epoxides bind covalently to macromolecules, especially DNA. These intermediates may be more toxic than the original form. Aryl hydrocarbon hydroxylase, encoded by cytochrome P450 1A1(*CYP1A1*) gene, is a well studied phase I enzyme and is particularly relevant to the metabolism of chemicals in cigarette smoke; *CYP1A1* gene is highly polymorphic in the population(16,17) and their polymorphisms have been associated with their encoded enzyme activities(18). Interindividual differences in susceptibility to the adverse health effects of cigarette smoke are in part attributable to different genotypes associated with these enzymes(19).

In china, the prevalence of tobacco use is much higher among men than women, for example, a 1996 national study of smoking prevalence found that 70 percent of men but only 4 percent of women currently smoked. However, 70 percent of nonsmoking Chinese women between the ages of 20 and 50 years reported exposure to passive smoke. Among exposed women, 72 percent reported that their passive smoke exposure occurred daily. Among women reporting passive smoke exposure in the national Chinese survey, 82 percent reported exposure at home compared with 28 percent in public places and 19 percent at work(20). This setting provides a good opportunity to study the effect of passive smoking exposure on dysmenorrhea. We hypothesized that among women who were passively exposed to tobacco smoke, a panel of genetic susceptibility factors including metabolic enzyme activities would influence the level of toxic substrates reaching the blood and further affect the dysmenorrhea. In this report, *CYP1A1* MspI and HincII gene polymorphisms are used to characterize genetic susceptibility and to assess the interaction between metabolic gene and passive cigarette smoking. Using data from a large prospective cohort study in Anqing, China.

## Materials and Methods

### Study sites and population

The current study is part of a prospective reproductive health study among women textile workers from 1997 to 2000 in Anqing, China, which is an urban area located ~200 km west of Shanghai. The study protocols were approved by the Human Subject Committee of Beijing Medical University and by the institutional review board of the Harvard School of Public Health. All employees of the textile mills received health care, including prenatal, delivery and postnatal care, in the affiliated hospital. The eligibility criteria for women in the

field enrollment were as follows: [1] full-time employed women workers; [2] newly married; [3] aged 20 to 34 years; and [4] had obtained permission to have a child. All the women were nulliparous. Women were excluded if they were already pregnant before enrollmen.

## Procedures

We used the Chinese marriage registration system to identify newly wed couples and those planning a first pregnancy. Upon enrollment, physical examination was performed, and height and weight were measured according to a standard protocol. A structured baseline questionnaire was administered by a trained interviewer to all the women and their husbands at enrollment to collect information concerning occupational exposures, personal habits such as cigarette smoking and alcohol consumption, living environment, exposure to passive smoking, dietary intake, menstrual and reproductive history, and contraceptive use. Blood samples were obtained from women via venipuncture by a skilled phlebotomist.. We obtained written informed consent from each woman. The genomic DNA was extracted according to standard protocol(21).

## Assessment of dysmenorrhea

From the baseline questionnaire, menstrual pain was defined as abdominal pain or low back pain during menstrual bleeding. In this report, dysmenorrhea was defined as 2 or more days of menstrual pain during menstrual bleeding in the most recent cycle.

## Assessment of passive smoking

The information on passive smoking was based on women self-reporting and was obtained from baseline questionnaire. Each woman recorded the mean number of cigarettes smoked per day at home by the regular household members. In our study, the specific question in the questionnaire was, “On average, what is the number of cigarettes someone smoked indoors at home while you were exposed per day in last month?” Exposure to tobacco smoke at workplace was not considered because any employee of the textile mills was not allowed to smoke. In the subsequent analysis, the passive smoking at home was considered as both a binary and an ordered tricotomous variable. We defined “non-passive smoking” as none of regular household members smoked at home and “passive smoking” as regular household members smoked at home.

## Genotyping

### Detection of the cytochrome P450 1A1 (CYP1A1) HincII(rs1048943) polymorphism—

*CYP1A1* HincII polymorphism was analysed according to Katoh et al (22). Primers used for the amplification were 5’-GTCTCCCTCTGGTTACAGGA-3’ and 5’-GAA AGACCT CCCAGC-GGTCA-3’. Digestion with the HincII for 3–4 h at 37°C resulted in diagnostic fragments visualized by ethidium bromide staining and ultraviolet transillumination after electrophoresis on a 5% polyacrylamide gel. This process resulted in 139, 120, 32, and 19 bp PCR products and was able to detect all 3 possible genotypes for the polymorphism: Ile/Ile462 (homozygous wild type), Ile/Val462 (heterozygous variant type), and Val/Val 462 (homozygous variant type). Homozygous wild type showed 139-and 32-bp fragments, while heterozygous variant type showed four bands at 139-, 120-, 32-, and 19-bp, respectively. Homozygous variant type showed only 120-, 32-, and 19-bp bands.

### Detection of the Cytochrome P450 1A1 (CYP1A1) MspI(rs4646420) Polymorphism—

The detailed method for detection of *CYP1A1* MspI polymorphism can be found elsewhere(18). Primers used for initial PCR amplification were 5’-TCACTCGTCTAAATACTCACCCTG-3’and 5’-AGGAGTCTTGTCTCATGCC T-3’.

After initial PCR amplification of this product, additional primers "nested" within the first product were used for reamplification. The two primers used the second set were 5'-CAGTGAAGAGGTGTAGCCGCT-3' and 5'-GAGGCA GGTG GATCACTTGAGCTC-3', respectively. Digestion with the *MspI* for 3–4 hours at 37°C resulted diagnostic fragments visualized by ethidium bromide staining and ultraviolet transillumination after electrophoresis on a 2% agarose gel. This process resulted in 295-, 160-, and 135-bp PCR products and was able to detect all 3 possible genotypes for the polymorphism: T/T6235 (homozygous wild type), T/C6235 (heterozygous variant type), and C/C6235 (homozygous variant type).

### Statistical methods

We use multiple logistic regression models to estimate the individual and combined associations of passive cigarette smoking and *CYP1A1* MspI and HincII genotypes in relation to dysmenorrhea with adjustment of major covariates. We investigated whether the association between passive smoking and dysmenorrhea is modified by *CYP1A1* genotypes by estimating the association between passive smoking and dysmenorrhea in stratified subgroups by the specific *CYP1A1* genotypes. To further assess gene-environment interaction, we examined the combined association of passive smoking and *CYP1A1* genotypes with dysmenorrhea in twelve subgroups defined by passive smoking status (no, yes) and *CYP1A1* genotypes for MspI (T/T6235, T/C6235, C/C6235) and HincII (Ile/Ile462, Ile/Val462/Val/Val462).

All the analysis were adjusted for the perceived stress(no, yes)confounder. All *p* values were 2-sided and defined as $P$=0.05 for statistical significance. We use statistical software SAS (SAS Institute Inc, Cary, NC) for all analysis.

## Results

The data for analysis included 1645 subjects (521 with dysmenorrhea and 1124 without such a status). Table 1 shows the characteristics for women with dysmenorrhea and women without dysmenorrhea, and also provided inferential statistics, that is, odds ratios and 95 percent confidence intervals for the discrete variables. The two groups were similar in terms of age, BMI, age of menarche, education, vibration exposure, shift work, noise exposure, pregnancy history and physical labor stress. Women with dysmenorrhea tended to have more perceived stress ($p$=0.033) and more likely to be passive smokers ($p$=0.002) than their counterparts.

Table 2 presents adjusted OR of dysmenorrhea in relation to passive smoking exposure stratified by *CYP1A1*HincII genotypes. The estimated association of passive smoking exposure with dysmenorrhea differed by genotypes in *CYP1A1*HincII. In model 1, the adjusted OR of dysmenorrhea was 1.6 (95%CI=1.3-2.1) for passive smoking group with Ile/Ile462 genotype compared to non passive smoking group. In model 2, passive smoking exposure was treated as an ordered tricotomous variable, adjusted OR of dysmenorrhea was 1.7 (95%CI=1.3-2.2) and 2.1 (95%CI=1.2-3.5) for 1-20 and >20 group with Ile/Ile462 genotype, respectively.

Table 3 presents adjusted OR of dysmenorrhea in relation to passive smoking exposure stratified by *CYP1A1*MspI genotypes. The estimated association of passive smoking exposure with dysmenorrhea differed by genotypes in *CYP1A1*MspI. In model 1, the adjusted OR of dysmenorrhea was 1.5 (95%CI=1.1-2.1) for passive smoking group with C/C6235 genotype compared to non passive smoking group. In model 2, passive smoking exposure was treated as an ordered tricotomous variable, adjusted OR of dysmenorrhea was

1.5 (95%CI=1.0-2.1) and 2.1(95%CI=1.1-3.9) for 1-20 and >20 group with C/C6235 genotype, respectively.

As shown in table 4, we further assessed the combined association of passive smoking exposure and *CYP1A1* genotypes with dysmenorrhea. In the absence of passive smoking exposure, none of the female genotypes was significantly associated with dysmenorrhea. However, in the presence of passive smoking exposure, there was a significant association with the *CYP1A1*Msp1 C/C6235 and HincII Ile/Ile462 genotype (OR=2.6, 95%CI=1.3-5.2).

## Discussion

This study has showed several interesting findings. Passive smoking was significantly associated with dysmenorrhea. In addition, both the Ile/Ile462 in *CYP1A1*HincII and C/C6235 in *CYP1A1*MspI were significantly associated with dysmenorrhea. When Passive smoking and *CYP1A1* genotypes were considered together, the largest association was found on passive smoking women with Ile/Ile462 in *CYP1A1*HincII and C/C6235 in *CYP1A1*MspI, among the nonexposed group, *CYP1A1* genetic susceptibility alone did not contribute to a significant adverse effect, suggesting that *CYP1A1* genotypes would modify the effect of passive smoking on dysmenorrhea.

This study has several unique features. It is one of the few studies to examine passive smoking in relation to dysmenorrhea, with regard to the role of genetic susceptibility in evaluating adverse effects of passive smoking on dysmenorrhea. It is based on a great number of female workers from Anqing, China where epidemiologic and clinical data were collected with a validated questionnaire and consistent methods by trained research workers and where passive smoke was determined by quantity and quality indexes. It is a population (nonsmoking, nondrinking), which offers an opportunity to test the gene-passive smoke interaction without substantial sociodemographic and environmental confounders, also, we analyzed our data to control confounding factor with stratification in possible direction, although the magnitude of the association was small, it is maybe more clearly to explain how passive smoking exposure affects dysmenorrhea involved genetic susceptibility.

Several previous reports have examined genetic polymorphisms and the risk of dysmenorrhea. An Australian twin study suggested that Genetic factors accounted for 39% of the longitudinally stable variation in menstrual flow, for 55% of pain, and for 77% of limitation by the menstrual pain(23). Wu D et al. found that both variant CYP2D6 and GSTM1 genotypes were associated with increased risk of recurrent dysmenorrhea(24). When both the *CYP2D6* and *GSTM1* genotypes were considered together, the highest risk of recurrent dysmenorrhea was found among women with variant genotypes in both *CYP2D6* and *GSTM1*. Another study showed that after potential confounders were adjusted, *CYP1A1*HincII variant had the trend of decreasing the risk of dysmenorrhea and the *GSTT1* variant genotypes showed a significantly increased risk of dysmenorrhea(25).

To our knowledge, although there are no published data on genetic susceptibility to passive cigarette smoking in relation to dysmenorrhea, this susceptibility is biologically plausible. Persons exposed to environmental tobacco smoke are subjected to most of the same constituents as those contained in mainstream smoke, but the pattern and amounts of exposure differ(26). The potential passive smoke mechanisms are essentially the same as those for active smoking(10, 27), including vasoconstriction and reduced endometrial blood flow due to nicotine, which is common in women with painful menses(9). Crofts et al. found that variant genotypes at the HincII site were significantly associated with increased *CYP1A1* gene inducibility(28). They also observed a significant interaction between the HincII polymorphism and smoking at the mRNA level. Consistently, our study found that

the passive smoking women who had *CYP1A1* MspI variant genotype C/C6235 or *CYP1A1* HincII wild genotype Ile/Ile462, which results in reduction of the individual's ability to convert toxic metabolites of cigarette smoke to less harmful hydrophilic compound, had significantly the higher risk of dysmenorrhea compared with the reference groups. Furthermore, the more women exposed to amount of passive smoking, the more remarkablely risk in C/C6235 group of *CYP1A1* MspI and Ile/Ile462 group of *CYP1A1* HincII, suggesting a dose-response relationship between passive smoking and dysmenorrhea. Our findings show the evidence that the interindividual differences in susceptibility to the adverse health effects of passive cigarette smoking are in part attributable to different women's genotypes of *CYP1A1*, and indicate that the women with C/C6235 genotype in *CYP1A1* MspI and Ile/Ile462 genotype in *CYP1A1* HincII are more susceptible to passive cigarette smoking and consequently tend to have the higher risk of dysmenorrhea.

Our study had several methodologic limitations. First, we did not have biochemical measurements of passive smoking exposure. Second, dysmenorrhea was measured by self-report. We did not further analyze subgroups of recurrent/severe dysmenorrhea or the timing of passive smoking exposure within a specific menstrual cycle in relation to the risk of dysmenorrhea. Third, our measurement of potential confounders was based on self-report rather than objective measurements, which may have limited our ability to control some confounders. Forth, There is an argument that traditional alpha values (e.g., 0.05) are insufficiently stringent for studies of genetic association. In the case of genome-wide linkage studies, the LOD score accepted as reflecting significant linkage is equivalent to an alpha level of <0.0005 (29). The significant results in our present study are marginal even if a conventional alpha of 0.05 is employed. Furthermore, such results were no longer statistically significant after Bonferroni correction. Hence, we do not exclude the possibility that the reported association in the present study may reflect false positive results (Type I error) due to the relative low statistical power. In addition, the association between genetic susceptibility to passive smoking and dysmenorrhea found in this study may be causal, may be a marker for other unknown genes or biologic pathways, or may be due to confounding by other unmeasured toxins or risk factors. Although our findings from observational study are biologically plausible and highly consistent, they are only suggestive, not conclusive. Further studies are needed to validate our findings.

## Conclusions

In summary, we have demonstrated that passive smoking is associated with dysmenorrhea. Such an association, however, is modified by an individual's genotype. This study provides evidence of combined effects of gene-environment and supports the importance of further assessing the role of genetic susceptibility in the evaluation of reproductive toxins. It has important implications for women's reproductive health.

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**Table 1**

Characteristics of the study population by dysmenorrhea status

| Characteristics | Dysmenorrhea(N%) No (N=1124) | Yes (N=521) | OR(95%CI) | *p* |
|---|---|---|---|---|
| Age(years) | | | | |
| <24† | 166(14.8) | 64(12.3) | 1 | --- |
| 24~28 | 763(67.9) | 371(71.2) | 1.3(0.9~1.7) | 0.147 |
| >28 | 195(17.3) | 86(16.5) | 1.1(0.8~1.7) | 0.493 |
| BMI | | | | |
| <20† | 391(34.8) | 175(33.6) | 1 | --- |
| 20~25 | 585(52.0) | 266(51.1) | 1.0(0.8~1.3) | 0.893 |
| >25 | 148(13.2) | 80(15.4) | 1.2(0.9~1.7) | 0.255 |
| Age of menarche (years) | | | | |
| <13† | 331(29.4) | 170(32.6) | 1 | ---- |
| 13~15 | 564(50.2) | 249(47.8) | 0.9(0.7~1.1) | 0.212 |
| >15 | 229(20.4) | 102(19.6) | 0.9(0.6~1.2) | 0.348 |
| Educational level | | | | |
| <Middle school† | 465(41.4) | 207(39.7) | 1 | --- |
| High school | 462(41.1) | 219(42.0) | 1.1(0.8~1.3) | 0.592 |
| >High school | 197(17.5) | 95(18.2) | 1.1(0.8~1.5) | 0.595 |
| Exposure to vibration | | | | |
| No† | 1007(89.6) | 464(89.1) | 1 | --- |
| Yes | 117(10.4) | 57(10.9) | 1.1(0.8~1.5) | 0.745 |
| Shift work | | | | |
| No† | 468(41.6) | 215(41.3) | 1 | --- |
| Yes | 656(58.4) | 306(58.7) | 1.0(0.8~1.3) | 0.887 |
| Exposure to noise | | | | |
| No† | 754(67.1) | 332(63.7) | 1 | --- |
| Yes | 370(32.9) | 189(36.3) | 1.2(0.9~1.4) | 0.181 |
| Perceived Stress | | | | |
| No† | 880(78.3) | 383(73.5) | 1 | --- |
| Yes | 244(21.7) | 138(26.5) | 1.3(1.0~1.7) | 0.033 |
| History of pregnancy | | | | |
| no† | 741(65.9) | 346(66.4) | 1 | --- |
| yes | 383(34.1) | 175(33.6) | 1.0(0.8~1.2) | 0.847 |
| Physical labor stress | | | | |
| light† | 534(47.5) | 233(44.7) | 1 | --- |
| moderate | 471(41.9) | 227(43.6) | 1.1(0.9~1.4) | 0.377 |
| heavy | 119(10.6) | 61(11.7) | 1.2(0.8~1.7) | 0.36 |
| Passive smoking | | | | |

| Characteristics | Dysmenorrhea(N%) | | OR(95%CI) | *p* |
|---|---|---|---|---|
| | No (N=1124) | Yes (N=521) | | |
| No† | 611(54.4) | 241(46.3) | 1 | --- |
| Yes | 513(45.6) | 280(53.7) | 1.4(1.1~1.7) | 0.002 |
| Cigarettes of passive smoking | | | | |
| 0† | 626(55.7) | 245(47.0) | 1 | --- |
| 1~20 | 437(38.9) | 236(45.3) | 1.4(1.1~1.7) | 0.004 |
| >20 | 61(5.4) | 40(7.7) | 1.7(1.1~2.6) | 0.017 |

†Reference category.

**Table 2**

Association of passive smoking with dysmenorrhea stratified by genotypes of CYP1A1HincII[a]

| *CYP1A1*HincII | Passive Smoking | Dysmenorrhea | | | |
|---|---|---|---|---|---|
| | | N(%) | OR* | 95%CI | *p* |
| | | Model 1 | | | |
| Val/Val462† | No | 9(22.5) | 1.0 | --- | --- |
| | Yes | 5(17.2) | 0.8 | 0.2~2.7 | 0.677 |
| Ile/Val462† | No | 91(31.7) | 1.0 | --- | --- |
| | Yes | 93(33.1) | 1.1 | 0.7~1.5 | 0.736 |
| Ile/Ile462† | No | 141(26.9) | 1.0 | --- | --- |
| | Yes | 182(37.7) | 1.6 | 1.3~2.1 | <0.001 |
| | | Model 2 | | | |
| Val/Val462† | 0 | 9(22.5) | 1.0 | --- | --- |
| | 1~20 | 4(14.8) | 0.6 | 0.2~2.4 | 0.513 |
| | >20 | 1(50.0) | 3.8 | 0.2~69.6 | 0.363 |
| Ile/Val462† | 0 | 94(31.8) | 1.0 | --- | --- |
| | 1~20 | 79(33.2) | 1.1 | 0.7~1.5 | 0.725 |
| | >20 | 11(32.4) | 1.0 | 0.5~2.2 | 0.951 |
| Ile/Ile462† | 0 | 142(26.5) | 1.0 | --- | --- |
| | 1~20 | 153(37.5) | 1.7 | 1.3~2.2 | <0.001 |
| | >20 | 28(43.1) | 2.1 | 1.2~3.5 | 0.006 |

*Estimates were derived from logistic regression models with adjustment for perceived stress.

†Reference category.

[a]Ile/Ile462 indicates homozygous wild type, Ile/Val462 indicates heterozygous variant type, and Val/Val 462 indicates homozygous variant type.

**Table 3**

Association of passive smoking with dysmenorrhea stratified by genotypes of CYP1A1MspI[a]

| *CYP1A1*MspI | Passive Smoking | Dysmenorrhea | | | |
|---|---|---|---|---|---|
| | | N(%) | OR* | 95%CI | *p* |
| | | Model 1 | | | |
| T/T6235† | No | 22(24.7) | 1.0 | --- | --- |
| | Yes | 19(25.7) | 1.1 | 0.5~2.1 | 0.913 |
| T/C6235† | No | 120(27.8) | 1.0 | --- | --- |
| | Yes | 137(33.7) | 1.3 | 1.0~1.8 | 0.056 |
| C/C6235† | No | 99(29.8) | 1 | --- | --- |
| | Yes | 124(39.6) | 1.5 | 1.1~2.1 | 0.011 |
| | | Model 2 | | | |
| T/T6235† | 0 | 22(24.4) | 1.0 | --- | --- |
| | 1~20 | 18(26.9) | 1.1 | 0.5~2.3 | 0.739 |
| | >20 | 1(16.7) | 0.5 | 0.1~5.0 | 0.585 |
| T/C6235† | 0 | 123(27.6) | 1.0 | --- | --- |
| | 1~20 | 116(33.9) | 1.4 | 1.0~1.9 | 0.047 |
| | >20 | 18(36.0) | 1.5 | 0.8~2.7 | 0.210 |
| C/C6235† | 0 | 100(29.8) | 1.0 | --- | --- |
| | 1~20 | 102(38.6) | 1.5 | 1.0~2.1 | 0.027 |
| | >20 | 21(46.7) | 2.1 | 1.1~3.9 | 0.024 |

*Estimates were derived from logistic regression models with adjustment for perceived stress.

†Reference category.

[a]T/T6235 indicates homozygous wild type; T/C6235 indicates heterozygous variant type; C/C6235 indicates homozygous variant type.

**Table 4**

Combined association of passive smoking exposure and CYP1A1MspI and CYP1A1HincII genotypes with dysmenorrhea[≠]

| Passive Smoking | MspI | HincII | Dysmenorrhea | | | |
|---|---|---|---|---|---|---|
| | | | N(%) | OR* | 95%CI | *P* |
| No[†] | T/T6235 | Ile/Val462 or Val/Val462 | 11(21.6) | 1.0 | --- | --- |
| No | T/T6235 | Ile/Ile462 | 11(28.9) | 1.5 | 0.6~3.9 | 0.426 |
| No | T/C6235 | Ile/Val462 or Val/Val462 | 69(30.8) | 1.6 | 0.8~3.3 | 0.193 |
| No | T/C6235 | Ile/Ile462 | 51(24.6) | 1.2 | 0.6~2.5 | 0.646 |
| No | C/C6235 | Ile/Val462 or Val/Val462 | 20(38.5) | 2.3 | 1.0~5.4 | 0.064 |
| No | C/C6235 | Ile/Ile462 | 79(28.2) | 1.4 | 0.7~2.9 | 0.328 |
| Yes | T/T6235 | Ile/Val462 or Val/Val462 | 10(19.6) | 0.9 | 0.3~2.3 | 0.807 |
| Yes | T/T6235 | Ile/Ile462 | 9(39.1) | 2.3 | 0.8~6.8 | 0.120 |
| Yes | T/C6235 | Ile/Val462 or Val/Val462 | 71(34.6) | 1.9 | 0.9~4.0 | 0.077 |
| Yes | T/C6235 | Ile/Ile462 | 66(32.8) | 1.8 | 0.9~3.7 | 0.122 |
| Yes | C/C6235 | Ile/Val462 or Val/Val462 | 17(31.5) | 1.7 | 0.7~4.0 | 0.253 |
| Yes | C/C6235 | Ile/Ile462 | 107(41.3) | 2.6 | 1.3~5.2 | 0.010 |

*Estimates were derived from logistic regression models with adjustment for perceived stress.

†Reference category.

≠T/T6235 indicates homozygous wild type; T/C6235 indicates heterozygous variant type; C/C6235 indicates homozygous variant type; Ile/Ile462 indicates homozygous wild type, Ile/ Val462 indicates heterozygous variant type, and Val/Val 462 indicates homozygous variant type.