Association between CYP1A1 Gene Polymorphisms and Cervical Cancer Susceptibility: A Meta-Analysis

Type
Research paper

Keywords
cervical cancer, meta-analysis, CYP1A1, MspI polymorphism, Ile462Val polymorphism

Abstract
Introduction
This study is to systemically analyze the association of CYP1A1 gene MspI and Ile462Val polymorphisms with cervical cancer susceptibility.

Material and methods
The literatures about the associations between CYP1A1 polymorphism and cervical cancer were retrieved through PubMed, Embase, Chinese biomedical literature database, Wanfang database, Database of Chinese Scientific and Technical Periodicals (VIP) and China Knowledge Network. Hardy-Weinberg equilibrium test was used to evaluate the quality of the included studies, and the data in the studies selected were analyzed by Stata 12.0 software. Potential publication bias was assessed with funnel plots and a modified Egger's linear regression test.

Results
A total of 17 studies were enrolled in this analysis. There were 14 articles on MspI locus polymorphism, including 2448 cases and 2520 controls. We found significant association between MspI locus polymorphism and cervical cancer susceptibility (C vs. T, OR 1.333, 95% CI 1.214-1.464, P≤0.001; CC vs. TT, OR 1.962, 95% CI 1.571-2.450, P≤0.001; CC/CT vs. TT, OR 1.591, 95% CI 1.406-1.800, P≤0.001; CC vs. TT/CT, OR 1.429, 95% CI 1.177-1.736, P≤0.001). Totally, 11 articles, including 2137 cases and 2116 controls, analyzed the Ile462Val locus polymorphism and the risk of cervical cancer. The result showed significant association between Ile462Val locus polymorphism and cervical cancer susceptibility (Val vs. Ile, OR 1.338, 95% CI 1.199-1.493, P≤0.001; ValVal vs. IleIle, OR 1.576, 95% CI 1.188-2.090, P=0.002; ValVal/IleIle vs. IleIle, OR 1.498; 95% CI 1.299-1.728, P≤0.001).

Conclusions
Both MspI and Ile462Val polymorphisms of CYP1A1 gene are associated with the risk of cervical cancer.
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Key words: cervical cancer; CYP1A1; MspI polymorphism; Ile462Val polymorphism; meta-analysis

Introduction

Cervical cancer is one of the most common gynecological malignancies. High-risk HPV infection is a risk factor for cervical cancer [1, 2]. In a cost-effectiveness study of different cervical screening approaches in developing countries, screening females once in a lifetime, at the age of 35 years, with a one- or two-visit screening strategy involving VIA or HPV testing reduced lifetime risk of cancer by approximately 25-36% [3]. However, less than 1% of HPV-infected patients suffer from cervical cancer, suggesting that early sexual activity, multiple partners, and frequent change of partners are also related with cervical cancer and that high-risk HPV infection is a necessary but
inadequate factor for cervical cancer [4-6]. Despite evidence showing protective effect of HPV vaccine against cervical cancer, it is still a dilemma whether to introduce this vaccine as a routine in several other countries as India, Sweden and Japan [7]. Smoking, drinking, long-term usage of oral contraceptives and other risk factors may also lead to the occurrence of cervical cancer [8, 9]. The identification of risk factors is critical for the treatment of cervical cancer and in-depth understanding of the disease.

The cytochrome P450 1A1 (CYP1A1) gene is a key member of the CYP1 family and is involved in the metabolism of endogenous and exogenous compounds in vivo. For example, the benzopyrene becomes an active and carcinogenic intermediate following CYP1A1 metabolism [10]. In addition, the phenylphosphatol estrogen is formed after catalyzed by CYP1A1, which further leads to the formation of ROS and DNA adducts and the occurrence of mutations during DNA replication [11-14]. Studies have shown that genomic instability caused by gene mutation and chromosome rearrangement is one of the most important factors for tumorigenesis [15-17]. It is reported that two loci polymorphisms of CYP1A1, CYP1A1 MspI (T3801C, rs4646903) and Ile462Val (A4889G, rs1048943), are closely related with cervical cancer [18-22]. Rs4646903 polymorphism locus is located in the 3' untranslated region, while the rs1048943 locus polymorphism is located on exon 7, whose mutation results in the substitution of amino acid at position 462 [23, 24]. Point mutations at rs4646903 and rs1048943 can lead to dysregulated CYP1A1 mRNA expression [17]. A number of studies have reported the association between the two loci polymorphisms and the
occurrence of cervical cancer in different ethnic groups, but the conclusions of different studies are still inconsistent [20, 21].

In this study, meta-analysis was used to evaluate the association of CYP1A1 rs4646903 and rs1048943 polymorphisms with cervical cancer. Our data may provide a basis for further study on the role of genetic factors in the pathogenesis of cervical cancer.

Materials and methods

Literature retrieval

Literatures reporting the association of CYP1A1 polymorphism and cervical cancer were retrieved through PubMed, Embase, Chinese biomedical literature database, Wanfang database, Database of Chinese Scientific and Technical Periodicals (VIP) and China Knowledge Network. The keywords for retrieval were ‘cytochrome P4501A1’ or ‘CYP1A1’ or ‘Ile462Val’ or ‘A4889G’ or ‘rs1048943’ or ‘MspI’ or ‘T3801C’ or ‘rs4646903’ and ‘cervical carcinoma’ or ‘cervical cancer’ or ‘cervix cancer’ At the same time, the reference list of the retrieved literatures was manually entered into the above mentioned databases to screen more suitable literatures.

Eligibility criteria
Studies were included in the meta-analysis if they met the following criteria: 1) They appeared online or in a peer-reviewed journal published in English or Chinese before 31 March 2017; 2) They were case–control studies; 3) The control group was healthy individuals; 4) Full text could be retrieved; 5) The distribution frequency of the CYP1A1 gene locus or the corresponding OR value is provided and the data is clearly expressed.

The exclusion criteria were as follows: 1) Articles with incomplete data; 2) Articles with cervical intraepithelial neoplasia or non-cervical cancer patients as research subjects; 3) The studies only researched the correlation between progress, severity, phenotypic modification, sensitivity to response to treatment, or survival with gene polymorphism; 4) Articles with family relevance analysis; 5) Repetitive reports or articles with poor quality or limited information.

Outcome indicator of this study is the incidence of cervical carcinoma.

Data extraction

Data were extracted by two authors independently. The disagreements were resolved by discussion or the third person. The following data were extracted from each study: year of publication, first author, the country where the study was performed, the ethnicity of participants, genotyping methods, genes and genotype data. We classified case selection as population-based if the study included data from different ethnicity, including Caucasian, Asians and others. Hardy–Weinberg equilibrium (HWE) test was
used to evaluate the quality of the enrolled studies.

Statistical analysis

Statistical analysis was performed with STATA version 12.0 (Stata Corporation, College Station, TX, USA). The Hardy-Weinberg equilibrium (HWE) in the controls was tested by the Chi-square test for goodness of fit. For the genetic variants, allelic, homozygous, dominant and recessive models were computed. Estimates of association between CYP1A1 polymorphism and cervical cancer were evaluated by odds ratios (ORs) and corresponding 95% confidence intervals (CIs). Heterogeneity between studies was assessed by the Cochran Q statistic and $I^2$ statistic. Generally, $P > 0.1$ and $I^2 < 25\%$ corresponds to heterogeneity; and $P < 0.1$ and $I^2 > 50\%$ corresponds to large heterogeneity. If the data were heterogeneous, a random effects model was adopted; if the data were homogeneous, a fixed effects model was applied. Potential publication bias was assessed with funnel plots and a modified Egger’s linear regression test was used to identify significant asymmetry. For all data, two-tailed tests were used throughout and $P < 0.05$ was considered significant.

Results

Basic information of included studies

A total of 130 articles were identified according to the keywords (Fig. 1). After
screened by title and abstract, 109 articles including 47 irrelevant articles, 41 articles with overlapping data, 4 reviews and 17 articles on animal or cells, were excluded. Thus, the remaining publications were screened by full text, identifying a total of 17 eligible articles that included 14 articles on MspI locus polymorphism [19-22, 25-34] and 11 on Ile462Val locus polymorphism [20, 25-28, 31-33, 35-37] of CYP1A1 gene. All articles included in the meta analysis were shown in Table I.

Meta analysis result for MspI

For the 14 articles on MspI locus polymorphism, 2248 patients and 2520 healthy controls were enrolled. As shown in Fig. 2, we found that MspI polymorphism of CYP1A1 gene was significantly associated with the susceptibility of cervical cancer (Fig. 2A; C vs. T, OR 1.333, 95% CI 1.214-1.464, P \( \leq \) 0.001) (Fig. 2B; CC vs. TT, OR 1.962, 95% CI 1.571-2.450, P \( \leq \) 0.001) (Fig. 2C; CC/CT vs. TT, OR 1.591, 95% CI 1.406-1.800, P \( \leq \) 0.001) (Fig. 2D; CC vs. TT/CT, OR 1.429, 95% CI 1.177-1.736, P = P \( \leq \) 0.001).

In the meta-analysis stratified by ethnicity, the MspI locus polymorphism was associated with cervical cancer among Caucasian women in allelic, homozygous and dominant models (C vs. T, OR 1.470, 95% CI 1.257-1.719, P \( \leq \) 0.001; CC vs. TT, OR 2.241, 95% CI 1.506-3.333, P \( \leq \) 0.001; CC/CT vs. TT, OR 1.650, 95% CI 1.344-2.025, P \( \leq \) 0.001). In homozygous, dominant and recessive models, the MspI locus polymorphisms was associated with cervical cancer among Asian women (CC vs. TT,
OR 1.603, 95% CI 1.194-2.153, P=0.002; CC/CT vs.TT, OR 1.450, 95% CI 1.224-1.717, P≤0.001; CC vs. TT/CT, OR 1.321, 95% CI 1.005-1.737, P=0.046) (Table II).

Meta analysis result for Ile462Val

There were 11 studies that analyzed the polymorphism at Ile462Val locus, including 2137 patients and 2116 healthy controls. As shown in Fig. 3, Ile462Val locus polymorphism of CYP1A1 gene was significantly associated with the risk of cervical cancer (Fig. 3A; Val vs. Ile, OR 1.338, 95% CI 1.199-1.493, P≤0.001) (Fig. 3B; ValVal vs. IleIle, OR 1.576, 95% CI 1.188-2.090, P=0.002) (Fig. 3C; ValVal/ValIle vs. IleIle, OR 1.498; 95% CI 1.299-1.728, P≤0.001). However, no correlation was found in recessive model (Fig. 3D; ValVal vs. IleIle/ValIle, OR 1.262; 95% CI 0.995-1.600, P=0.055).

Subgroup analysis by ethnicity found that the Ile462Val locus polymorphism had an association with the risk of cervical cancer among Caucasian women in allelic and dominant models (Val vs. Ile, OR 1.701, 95% CI 1.392-2.077, P≤0.001; ValVal/ValIle vs. IleIle, OR 1.405, 95% CI 1.247-1.583, P≤0.001). In allelic, homozygous and dominant models, Ile462Val locus polymorphism had associations with the risk of cervical cancer among Asian women (Val vs. Ile, OR 1.210, 95% CI 1.062-1.379, P=0.004; ValVal vs. IleIle, OR 1.575, 95% CI 1.156-2.146, P=0.004; ValVal/ValIle vs. IleIle, OR 1.313, 95% CI 1.101-1.565, P=0.002) (Table III).

Publication bias analysis
Publication bias was assessed by funnel plots and modified Egger’s tests, and no possible publication bias was found. The results of Egger’s test of MspI locus was C vs. T, \( P=0.219 \); CC vs. TT, \( P=0.127 \); CC/CT vs. TT, \( P=0.331 \); CC vs. TT/CT, \( P=0.631 \) (Fig. 4). The results of Egger’s test of Ile462Val locus was Val vs. Ile, \( P=0.891 \); ValVal vs. IleIle, \( P=0.233 \); ValVal/ValIle vs. IleIle, \( P=0.825 \); ValVal vs. IleIle/ValIle, \( P=0.279 \) (Fig. 5). Similar results were obtained by funnel plots (Fig. 6 & 7).

**Discussion**

Cervical cancer is still the most important gynecological malignancy in developing countries with incidence increasing year by year [38]. Cytochrome P450 1A1 mainly participate in the occurrence of cancer by regulating the metabolism of proteins, DNA, lipids and estrogens [39, 40]. A number of studies have reported the association between CYP1A1 gene polymorphism and the susceptibility to cervical cancer, but the conclusion is controversial due to the differences in the study design, the study population, the detection method and the sample size [19-22]. Therefore, the current study investigated the correlation between CYP1A1 gene polymorphism and cervical cancer susceptibility through meta-analysis on 17 studies.

A total of 14 articles on MspI locus polymorphism were enrolled in our study, which comprised 2448 patients and 2520 healthy controls. Analysis results of allelic, homozygous, dominant and recessive models all indicate that MspI locus polymorphism of CYP1A1 gene is closely associated with the risk of cervical cancer. This result is in
accordance with a meta-analysis on the relationship between MspI locus polymorphism and cervical cancer by Xia et al. [41]. Additionally, analysis stratified by ethnicity showed the association of MspI locus polymorphism and the risk of cervical cancer in Caucasian women and Asian women in multiple genetic variants. However, a study by Theodoros et al. failed to identify any association between MspI locus polymorphism and the cervical cancer susceptibility among Asian women, in which only 3 articles on Asian population were included [42]. We suppose that the result of our study is relatively more accurate because the small number of studies on Asian women in their study may increase the inaccuracy the meta-analysis conclusion.

For meta-analysis of Ile462Val locus polymorphism, 11 articles including 2137 cervical cancer patients and 2116 healthy controls were enrolled. We found that Ile462Val locus polymorphism of CYP1A1 gene was significantly associated with the risk of cervical cancer. Subgroup analysis by ethnicity showed that the Ile462Val locus polymorphism was associated with the risk of cervical cancer among Caucasian women in allelic and dominant models, while among Asian women in allelic, homozygous and dominant models. Generally our results are similar to those of Yang et al. and Theodoros et al. [42, 43]. However, their study did not report the association between Ile462Val locus polymorphism and cervical cancer susceptibility in Asian population. We speculate that the difference in result may due to differences in the number of selected articles as well as the number of cases [42, 43]. Further meta-analysis with larger samples is still needed to obtain a more accurate conclusion for the association
between Ile462Val locus polymorphism and cervical cancer susceptibility in Asian women.

Previous studies have reported differences in the association between CYP1A1 gene MspI locus polymorphism and susceptibility to different cancers [42, 44, 45]. In addition, the Ile462Val polymorphism is closely related to the risk of ovarian cancer, lung cancer and liver cancer, but is not related to the risk of gastric cancer and breast cancer [44-48]. Here, in the current meta-analysis, we found that both MspI and Ile462Val locus polymorphisms were associated with the risk of cervical cancer, indicating that these polymorphisms may have distinctive roles in different kinds of cancer. This may be caused by the specific CYP1A1 functions in different tissues or cells.

The present study had some limitations. First, data on the family history, smoking, drinking, age and other environmental exposure factors was lacking for the enrolled articles. Thus, non-adjusted ORs were obtained. Second, due to the lack of adequate pathological data, stratified analysis could not be done based on pathological types. Third, there was heterogeneity between the included literatures. Fourth, this study failed to analyze the interactions between genes and genes or genes and the environment and their impact on the association between gene polymorphisms and cancer.
Conclusions

In summary, this meta-analysis demonstrates that the MspI and Ile462Val polymorphisms of CYP1A1 gene are involved in the development of cervical cancer. To further verify such association, studies with larger number of samples, accurate sample information and reasonable study designs are warranted.
Conflicts of Interest

The authors declares that there is no conflict of interest regarding the publication of this paper.
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Figure legends

Figure 1. Study flow chart explaining the selection of the seventeen eligible case control articles enrolled in the meta-analysis.

Figure 2. Significant association between CYP1A1 MspI polymorphism and the risk of cervical cancer as determined by (A) allele model (C vs. T, \( P=0.000 \)); (B) homozygote model (CC vs. TT, \( P=0.000 \)); (C) dominant model (CC/CT vs. TT, \( P=0.000 \)) and (D) recessive model (CC vs. TT/CT, \( P=0.000 \)).

Figure 3. Significant association between CYP1A1 Ile462Val polymorphism and the risk of cervical cancer as determined by (A) allele model (Val vs. Ile, \( P=0.000 \)), (B) homozygote model (ValVal vs. IleIle, \( P=0.009 \)), (C) dominant model (ValVal/ValIle vs. IleIle, \( P=0.000 \)) and (D) recessive model (ValVal vs. IleIle/ValIle, \( P=0.055 \)).

Figure 4. Egger’s test on MspI polymorphism did not show any obvious evidence of
publication bias in all genetic models. (A) allele model (C vs. T, \( P=0.219 \)); (B) homozygote model (CC vs. TT, \( P=0.127 \)); (C) dominant model (CC/CT vs. TT, \( P=0.331 \)) and (D) recessive model (CC vs. TT/CT, \( P=0.631 \)).

Figure 5. Egger’s test on Ile462Val polymorphism did not show any obvious evidence of publication bias in all genetic models. (A) allele model (Val vs. Ile, \( P=0.891 \)), (B) homozygote model (ValVal vs. IleIle, \( P=0.233 \)), (C) dominant model (ValVal/ValIle vs. IleIle, \( P=0.825 \)) and (D) recessive model (ValVal vs. IleIle/ValIle, \( P=0.279 \)).

Figure 6. Funnel plots of MspI polymorphism did not show any obvious evidence of publication bias in all genetic models. (A) allele model (C vs. T); (B) homozygote model (CC vs. TT); (C) dominant model (CC/CT vs. TT) and (D) recessive model (CC vs. TT/CT).

Figure 7. Funnel plots of Ile462Val polymorphism did not show any obvious evidence of publication bias in all genetic models. (A) allele model (Val vs. Ile), (B) homozygote model (ValVal vs. IleIle), (C) dominant model (ValVal/ValIle vs. IleIle) and (D) recessive model (ValVal vs. IleIle/ValIle).
Table I. Quality scores of literatures included in the meta-analysis.

| Author (year)          | Ethnicity | Study design | Polymorphisms studied | Genotype method | HWE in controls |
|------------------------|-----------|--------------|------------------------|-----------------|-----------------|
| Kim(2000) [26]         | Asians    | HCS          | MspI                   | PCR-RFLP        | 0.05            |
| Sugawara(2003) [29]    | Asians    | HCS          | MspI, Ile462Val        | PCR-RFLP        | 0.23/0.28       |
| Taskiran(2006) [33]    | Caucasian | HCS          | Ile462Val              | PCR-RFLP        | 0.15            |
| Joseph(2006) [24]      | Caucasian | HCS          | MspI, Ile462Val        | PCR-RFLP        | 0.24/0.20       |
| Juarez-Cedillo(2007) [25] | others      | HCS          | MspI                   | PCR-RFLP        | 0.64            |
| Li(2009) [27]          | Asians    | HCS          | MspI, Ile462Val        | PCR-RFLP        | 0.56/0.36       |
| Gutman(2009) [23]      | Caucasian | HCS          | MspI, Ile462Val        | PCR-RFLP        | 0.39/0.30       |
| Geng(2010) [31]        | Asians    | HCS          | Ile462Val              | PCR-RFLP        | 0.01            |
| Shi (2011) [28]        | Asians    | HCS          | MspI, Ile462Val        | PCR-RFLP        | 0.87/0.25       |
| Ding (2011) [22]       | Asians    | HCS          | MspI, Ile462Val        | PCR-RFLP        | 0.04/0.003      |
| von(2011) [30]         | Caucasian | HCS          | MspI                   | PCR-RFLP        | 0.18            |
| Abbas (2014) [21]      | Caucasian | HCS          | MspI, Ile462Val        | PCR-RFLP        | 0.36/0.30       |
| Roszak(2014) [32]      | Caucasian | HCS          | Ile462Val              | PCR-RFLP        | 1.00            |
| Kleine(2015) [18]      | Caucasian | HCS          | MspI                   | PCR-RFLP        | 0.23            |
| Tan(2016) [17]         | Mixed     | HCS          | MspI                   | PCR-RFLP        | 0.94            |
| Matos(2016) [15]       | Caucasian | HCS          | MspI                   | PCR-RFLP        | 0.81            |
| Li(2016) [16]          | Asians    | HCS          | MspI, Ile462Val        | Taqman          | 0.79/0.84       |

HWE, Hardy-Weinberg equilibrium.
Table II. Meta-analysis of the association between CYP1A1 gene MspI polymorphism and cervical cancer risk.

| Contrast model       | Number of studies | Subjects (cases/controls) | OR(95%CI)         | P     | I²(%) |
|----------------------|-------------------|---------------------------|-------------------|-------|-------|
| Total studies        |                   |                           |                   |       |       |
| C vs. T              | 14                | 2448/2520                 | 1.333(1.214-1.464) | ≤0.001| 89.1  |
| CC vs. TT            | 14                | 2448/2520                 | 1.962(1.571-2.450) | ≤0.001| 76.7  |
| CC/CT vs. TT         | 14                | 2448/2520                 | 1.591(1.406-1.800) | ≤0.001| 79.2  |
| CC vs. TT/CT         | 14                | 2448/2520                 | 1.429(1.177-1.736) | ≤0.001| 75.6  |
| Subgroup analysis    |                   |                           |                   |       |       |
| Caucasians           |                   |                           |                   |       |       |
| C vs. T              | 7                 | 999/1137                  | 1.470(1.257-1.719) | ≤0.001| 91.0  |
| CC vs. TT            | 7                 | 999/1137                  | 2.241(1.506-3.333) | ≤0.001| 79.1  |
| CC/CT vs. TT         | 7                 | 999/1137                  | 1.650(1.344-2.025) | ≤0.001| 74.4  |
| CC vs. TT/CT         | 7                 | 999/1137                  | 1.225(0.905-1.658) | 0.190 | 84.2  |
| Asians               |                   |                           |                   |       |       |
| C vs. T              | 7                 | 1240/1163                 | 1.088(0.957-1.228) | 0.199 | 70.6  |
| CC vs. TT            | 7                 | 1240/1163                 | 1.603(1.194-2.153) | 0.002 | 61.6  |
| CC/CT vs. TT         | 7                 | 1240/1163                 | 1.450(1.224-1.711) | ≤0.001| 77.2  |
| CC vs. TT/CT         | 7                 | 1240/1163                 | 1.321(1.005-1.737) | 0.046 | 0.0   |
Table III. Meta-analysis of the association between CYP1A1 gene Ile462Val polymorphism and cervical cancer risk.

| Contrast model               | Number of studies | Subjects (cases/controls) | OR (95%CI)       | P       | I² (%) |
|------------------------------|-------------------|---------------------------|------------------|---------|--------|
| Total studies                |                   |                           |                  |         |        |
| Val vs. Ile                  | 11                | 2137/2116                 | 1.338(1.199-1.493) | ≤0.001  | 73.8   |
| ValVal vs. IleIle            | 11                | 2137/2116                 | 1.576(1.188-2.090) | 0.002   | 64.0   |
| ValVal/Valle vs. IleIle      | 11                | 2137/2116                 | 1.498(1.299-1.728) | ≤0.001  | 73.4   |
| ValVal vs. IleIle/ValIle     | 11                | 2137/2116                 | 1.262(0.995-1.600) | 0.055   | 64.8   |
| Subgroup analysis            |                   |                           |                  |         |        |
| Caucasians                   |                   |                           |                  |         |        |
| Val vs. Ile                  | 5                 | 931/1084                  | 1.701(1.392-2.077) | ≤0.001  | 71.2   |
| ValVal vs. IleIle            | 5                 | 931/1084                  | 1.580(0.794-3.145) | 0.193   | 28.2   |
| ValVal/Valle vs. IleIle      | 5                 | 931/1084                  | 1.405(1.247-1.583) | ≤0.001  | 96.3   |
| ValVal vs. IleIle/ValIle     | 5                 | 931/1084                  | 1.530(0.940-2.489) | 0.087   | 0.0    |
| Asians                       |                   |                           |                  |         |        |
| Val vs. Ile                  | 6                 | 1206/1032                 | 1.210(1.062-1.379) | 0.004   | 69.0   |
| ValVal vs. IleIle            | 6                 | 1206/1032                 | 1.575(1.156-2.146) | 0.004   | 77.8   |
| ValVal/Valle vs. IleIle      | 6                 | 1206/1032                 | 1.313(1.101-1.565) | 0.002   | 58.7   |
| ValVal vs. IleIle/ValIle     | 6                 | 1206/1032                 | 1.190(0.907-1.561) | 0.208   | 78.9   |
Articles identified through literature search (n=130)

Excluded after reviewing abstracts (n=109)
  - Overlapping records (n=41)
  - Obvious irrelevant studies (n=47)
  - Reviews (n=4)
  - Animal or cell experiments (n=17)

Full-text publications assessed for eligibility (n=21)

Without usable data (n=4)

Case-control studies on Mspl (n=14)

Case-control studies on Ile462Val (n=11)
## A

| Study     | OR (95% CI) | %  | Weight |
|-----------|-------------|----|--------|
| Kim(2005) | 1.05 (0.74, 1.50) | 10.94 |        |
| Suganuma(2003) | 1.24 (0.84, 1.84) | 2.13 |        |
| Joseph(2006) | 0.41 (0.25, 0.64) | 7.98 |        |
| James Castillo(2007) | 3.23 (2.29, 4.60) | 6.99 |        |
| Gunner(2008) | 0.77 (0.50, 1.20) | 1.40 |        |
| Ig(2005) | 1.24 (0.71, 2.16) | 2.60 |        |
| van(2011) | 1.33 (0.90, 1.94) | 6.17 |        |
| BN(2011) | 1.39 (0.98, 1.93) | 6.37 |        |
| Elg(2011) | 0.69 (0.43, 1.10) | 19.13 |        |
| Active(2010) | 1.03 (0.97, 1.09) | 8.75 |        |
| Watson(2010) | 4.10 (1.70, 9.46) | 2.04 |        |
| Ten(2010) | 1.34 (0.96, 1.87) | 7.51 |        |
| Malco(2014) | 2.93 (1.67, 4.98) | 2.94 |        |
| LC(2010) | 1.44 (1.13, 1.84) | 14.49 |        |
| Overall (I^2 = 89.1%, p < 0.001) | 1.33 (1.21, 1.48) | 100.00 |        |

## B

| Study     | OR (95% CI) | %  | Weight |
|-----------|-------------|----|--------|
| Kim(2005) | 1.19 (0.89, 1.60) | 12.99 |        |
| Suganuma(2003) | 3.18 (2.35, 4.35) | 13.98 |        |
| Joseph(2006) | 0.27 (0.10, 0.79) | 6.97 |        |
| James Castillo(2007) | 9.20 (0.26, 31.19) | 3.42 |        |
| Gunner(2008) | 0.85 (0.60, 1.20) | 1.73 |        |
| Ig(2005) | 1.84 (1.41, 2.41) | 5.38 |        |
| BN(2011) | 1.19 (0.87, 1.64) | 3.21 |        |
| Elg(2011) | 1.32 (0.63, 2.62) | 3.33 |        |
| Watson(2010) | 3.91 (1.70, 8.96) | 2.04 |        |
| Ten(2010) | 1.19 (0.92, 1.56) | 3.15 |        |
| Malco(2014) | 3.67 (1.33, 10.24) | 1.73 |        |
| LC(2010) | 4.08 (1.09, 15.03) | 1.73 |        |
| Overall (I^2 = 70.7%, p = 0.001) | 1.08 (0.97, 1.24) | 100.00 |        |

## C

| Study     | OR (95% CI) | %  | Weight |
|-----------|-------------|----|--------|
| Kim(2005) | 1.08 (0.70, 1.64) | 9.93 |        |
| Suganuma(2003) | 1.11 (0.65, 2.02) | 7.98 |        |
| Joseph(2006) | 0.25 (0.07, 0.94) | 2.50 |        |
| James Castillo(2007) | 8.27 (0.32, 233.32) | 1.16 |        |
| Gunner(2008) | 1.12 (0.38, 3.46) | 2.50 |        |
| Ig(2005) | 1.24 (0.80, 1.83) | 13.54 |        |
| van(2011) | 1.35 (0.87, 2.11) | 8.67 |        |
| BN(2011) | 1.39 (0.84, 2.36) | 8.67 |        |
| Elg(2011) | 2.64 (1.05, 6.61) | 7.60 |        |
| Active(2010) | 2.72 (1.01, 7.28) | 3.00 |        |
| Watson(2010) | 1.38 (0.83, 2.32) | 6.05 |        |
| Malco(2014) | 3.94 (1.46, 10.17) | 3.49 |        |
| LC(2010) | 2.35 (1.73, 3.42) | 12.64 |        |
| Overall (I^2 = 70.0%, p = 0.001) | 1.39 (1.21, 1.60) | 100.00 |        |

## D

| Study     | OR (95% CI) | %  | Weight |
|-----------|-------------|----|--------|
| Kim(2005) | 1.18 (0.94, 1.48) | 10.29 |        |
| Suganuma(2003) | 3.10 (2.59, 3.70) | 10.75 |        |
| Joseph(2006) | 0.28 (0.11, 0.71) | 20.68 |        |
| James Castillo(2007) | 4.78 (1.93, 10.70) | 3.87 |        |
| Gunner(2008) | 1.88 (1.21, 2.96) | 2.75 |        |
| Ig(2005) | 1.24 (0.80, 2.50) | 2.50 |        |
| BN(2011) | 1.49 (0.94, 2.47) | 2.50 |        |
| Elg(2011) | 1.05 (0.92, 1.20) | 1.00 |        |
| Active(2010) | 1.63 (1.21, 1.07) | 2.50 |        |
| Watson(2010) | 1.66 (1.04, 2.66) | 1.00 |        |
| Malco(2014) | 3.08 (0.80, 11.88) | 1.00 |        |
| LC(2010) | 2.24 (1.64, 2.49) | 1.00 |        |
| Overall (I^2 = 70.0%, p = 0.001) | 1.39 (1.21, 1.60) | 100.00 |        |
