Genetic polymorphisms of CYP2C9/CYP2C19 in chronic obstructive pulmonary disease

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Abstract

Background: Chronic obstructive pulmonary disease (COPD) has a high incidence in elderly and significantly affects the quality of life. CYP2C9 and CYP2C19 have an important role in tobacco-related diseases and inflammatory reaction. Thus, in this study we aims to investigate the association between CYP2C9 / CYP2C19 polymorphisms and the risk of COPD.

Methods: A total of 821 subjects were recruited which including 313 COPD patients and 508 healthy controls. Seven SNPs of CYP2C9 / CYP2C19 were selected for genotyping. The Odds ratios (ORs) and 95% confidence interval (95% CI) were calculated using a logistic regression analysis to evaluate the association between COPD risk and CYP2C9 / CYP2C19 polymorphisms.

Results: The rs9332220 of CYP2C9 "A" allele was associated with reducing COPD risk (OR = 0.64, 95% CI = 0.43 – 0.94, p = 0.021). And rs11853758 "G" allele carrier could significantly decrease 0.35-fold COPD risk compared with T allele carrier (OR = 0.65, 95% CI = 0.45 – 0.96, p = 0.027). Furthermore, gender-based stratification analysis showed that rs9332220 and rs11853758 polymorphisms were associated with risk of COPD in males.

Conclusions: Our study firstly reported the effects of CYP2C9 and CYP2C19 genetic variants on COPD risk. We found that rs9332220 in CYP2C9 and rs11853758 in CYP2C19 were associated with a reduced susceptibility to COPD.

Background

Chronic obstructive pulmonary disease (COPD) has a high incidence in elderly people and significantly affects the quality of life. The characterized of COPD is airflow limitation. That is an incompletely reversible chronic persistent inflammatory process. Smoking is the major environmental risk factor. Only 10-15% of smokers end up with COPD. The COPD is more common in people who have a COPD family history. The COPD was also showed a high risk in identical twins than fetal twins, which means genetic factor play a key role in COPD etiology. Therefore, to identify the genetic factor about smoking and inflammatory in COPD is beneficial to early prevention and accurate diagnosis of COPD.

The cytochrome P450 family 2 subfamily C (CYP2C) is a key player in the generation of EETs, the enzymes CYP2C9 and CYP2C19 are the major CYP2C involved in epoxyeicosatrienoic acids (EETs) production. The CYP2C19 metabolize arachidonic acid (AA) to produce EETs, the EETs anti-inflammatory actions possess an established protective effect on human cardiovascular system. The CYP2C9 enzymes have been detected not only in liver-located but also in lungs, pancreas, stomach and kidneys. CYP2C9 can metabolize polycyclic aromatic hydrocarbons in tobacco smoke and thereby generate disease-causing metabolites. Genetic variation in genes coding for CYP9C9 enzymes has shown changes in enzyme activity that affect metabolite levels, resulting in a potential risk of disease, suggesting that CYP2C9 plays a key role in tobacco-related diseases.

In consideration of the CYP2C9 and CYP2C19 have an important role in tobacco-related diseases and inflammatory reaction, therefore in this study we did the association study between the CYP2C9/CYP2C19 polymorphism and the risk of COPD. A total of four SNPs (rs10509679, rs1934967, rs1234968 and rs9332220) of CYP2C9 and three SNPs (rs111853758, rs4494250 and rs75665761) of CYP2C19 were enrolled in this study. This study may provide the new marker for diagnosis of COPD.

Methods

Study population

821 participants were recruited from the Hainan general hospital for genotyping, which included 313 COPD patients and 508 healthy controls. According to the related literature report, COPD patients were diagnosed based on the multiple examinations results including the ratio of forced expiratory volume in 1 second/forced vital capacity (FEV1/FVC ratio < 70% and FEV1 < 80% predicted). The healthy controls were collected from physical examination center of Hainan General Hospital and all of them exhibited normal pulmonary function (FEV1/FVC ratio > 70% and FEV1 > 80% predicted).

This study was approved by the ethics committee of Hainan General Hospital, and all participants signed the informed consent. The characteristic information of cases and controls were showed in Table 1.
Selection and genotyping of SNPs

Based on the database of 1000 genomes project (www.internationalgenome.org/), the SNP data of CYP2C9 and CYP2C19 were downloaded. Firstly, we chose the SNPs based on $r^2 > 0.8$, MAF > 0.05 in global population and the linkage disequilibrium of SNPs been detected by Haplovew software. Secondly, the primers of the selected SNPs were designed by Agena on-line software. Four SNPs (rs10509679, rs1934967, rs1234968 and rs9332220) of CYP2C9 and three SNPs (rs111853758, rs4494250 and rs75665761) of CYP2C19 linkage disequilibrium and well-designed primer SNPs were chosen.

Genomic DNA of all participants was extracted from peripheral blood using GoldMag-Mini whole blood genomic DNA purification kit (GoldMag Co. Ltd. Xi’an City, China). The Agena on-line software was used to design the primers (https://agenacx.com/online-tools/), and the primers of this study were listed in table 2. The genotyping of each SNP was detected by Agena MassARRAY platform (Agena Bioscience, SanDiego, CA, USA).

Statistical analysis

Age was displayed as mean ± standard deviation. The number of gender and smoking status were respectively statistics in cases and controls. Hardy-Weinberg equilibrium (HWE) of each SNP was evaluated by exact test. The $p$ value less than 0.05 were defined statistically significant. The odds ratios (ORs) and 95% confidence interval (95% CI) were calculated using a logistic regression analysis. The Microsoft Excel and PLINK software were used analysis the relationship between the COPD risk and SNPs.

Results

313 COPD patients and 508 healthy controls were enrolled in this study. The average age of cases was 60 years old and the controls were nearly 72 years old. The average age between cases and controls have a significant difference ($p < 0.001$). In order to reduce the influence of age on the results, we adjusted the age in the later analysis. We also collected the sex, smoking status, BMI index and FEV$_1$/FVC information of cases and controls (Table 1).

The basic information of SNPs from CYP2C9 and CYP2C19 were presented in Table 3. Rs9332220 “A” allele was associated with a reduced COPD susceptibility (OR = 0.64, 95% CI = 0.43 - 0.94, $p = 0.021$), at the same time, rs11853758 “G” allele carrier with significant decreased risk 0.35-fold of COPD compared with T allele carrier (OR = 0.65, 95% CI = 0.45 - 0.96, $p = 0.027$).

The SNPs rs9332220 and rs11853758 were associated with COPD susceptibility under allele model, but the association between SNPs rs9332220 and rs11853758 and COPD risk under various genetic models were not significant (data not shown). After adjusted for age and sex, we found that the SNP loci rs1934968 AA genotype was not associated with COPD under allele model but significant associated with COPD under recessive model (OR = 0.54, 95% CI = 0.30 - 0.96, $p = 0.037$, Table 4).

As is shown in Table 5, a gender-based stratification analysis was performed. SNP loci rs9332220 of CYP2C9 “A” allele compared with “G” allele were associated with an decreased risk of COPD in the males (OR = 0.59, 95% CI = 0.37 - 0.92, $p = 0.020$), SNP loci rs111853758 of CYP2C19 “G” allele carriers were also associated with decreasing risk of COPD under allele model (OR = 0.62, 95% CI = 0.40 - 0.96, $p = 0.032$), but another two SNPs were not associated with COPD risk in females.

Discussion

In current study, we found that the rs9332220 “A” allele of CYP2C9 and rs11853758 “G” allele of CYP2C19 apparently associated with a decreased risk of COPD based on 821 participants from Hainan population. Moreover, rs9332220 and rs11853758 may influence the COPD risk of males in gender stratification analysis.

COPD is a complex disease caused by interaction of environmental and genetic factors. Several environmental risk factors for COPD have been identified $^{16,17}$. While the genetic risk factors were less well understood. The cytochrome P450 proteins were catalyzed many reactions involved in drug metabolism and synthesis of cholesterol, steroids and other lipids $^{18,19}$. In the genetic polymorphisms of
cytochrome P450 in COPD, Chen et al. found that CYP1A1 is an independent risk factor for very severe COPD \(^{20}\). Yang et al. also reported that CYP1A1 polymorphisms were associated with COPD susceptibility \(^{21}\), and Wang et al meta-analysis proved that CYP1A1 polymorphism might play a role in COPD risk among Asian population\(^{22}\). Seo et al. suggested that CYP3A4 may be play a role in airway injury of smokers \(^{23}\). All CYP enzymes share a common structure and similar function in the same way \(^{11}\). Thus, the association between polymorphism of CYP2C9 and CYP2C19 and COPD were assessed in this study.

CYP2C9 and CYP2C19 gene were located within a cluster of cytochrome P450 genes on chromosome 10q24. Previous studies reported the polymorphisms of CYP2C9 and CYP2C19 and risk of coronary heart disease (CHD) in Russian population\(^{24}\). In one study, bladder cancer decreased risk was associated with CYP2C9 variant loci carriers \(^{25}\). Combined with this study, CYP2C9 not only associated with tobacco-related cancers but also associated with tobacco-related COPD. Kamata et al. noted an up-regulation of CYP2C19 mRNA expressions in Alveolar epithelial type II (ATII) cells isolated from patients with COPD compared with smokers without COPD \(^{26}\). Kamata et al.’s study may have important implications for the research of COPD pathogenesis. Our findings firstly revealed that rs11853758 of CYP2C19 was obviously related to COPD susceptibility.

The CYP epoxygenases catalyze the epoxidation of the intracellular AA that gives rise to corresponding EETs \(^{27}\). EETs have anti-inflammatory, antiapoptotic, and antioxidative activities, and autophagy is believed to be involved in the pathogenesis of COPD \(^{28}\). EETs may protect the heart and liver by regulating autophagy \(^{29}\). The SNPs rs9332220 and rs11853758 polymorphisms in CYP2C9 and CYP2C19 may regulate the epoxygenases activity and influence the EETs production. It may be protective property of COPD by inhibiting autophagy.

There are some limitations in our study. The sample size is relatively small. In the future, we need to expand the sample size to verify our results. It’s necessary to study how CYP2C9 and CYP2C19 polymorphism influence the underlying pathogenesis of COPD for further study. Despite the above limitations, our present works provide the available evidence of CYP2C9 and CYP2C19 gene with COPD for the future study.

Conclusions

In conclusion, our present work indicated that rs9332220 in CYP2C9 and rs11853758 in CYP2C19 were associated with a reduced susceptibility to COPD.

Abbreviations

COPD: Chronic obstructive pulmonary disease; ORs: Odds ratios; 95% CI: 95% confidence interval; CYP2C: Cytochrome P450 family 2 subfamily C; EETs: Epoxyeicosatrienoic acids; AA: Arachidonic acid; FEV\(_1\): Forced expiratory volume in 1 second; FVC: Forced vital capacity; HWE: Hardy-Weinberg equilibrium; CHD: Coronary heart disease; ATII: Alveolar epithelial type II; BMI: Body mass index.

Declarations

Ethics approval and consent to participate
All procedures performed in studies involving human participants were in accordance with the ethical standards of the Hainan General Hospital and with the 1964 Helsinki declaration. Informed consent was obtained from all individual participants included in the study.

Consent for publication
Not applicable.

Availability of data and materials
All the data regarding the findings are available within the manuscript. Anyone who is interested in the information should contact the corresponding author.
**Competing interests**

All authors declare that they have no competing interests.

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**Authors' contributions**

H L and YP: Conceived and designed the experiments. DC X, Q F, J S, QN L and J Z: Recruited and collected study samples. H N, P H and JF L: Selected the SNPs and designed primers. YX Y: Performed the data. H L: Wrote the manuscript. H L, YX Y and YP D: Contributed to data analysis and manuscript revised. All authors read and approved the final manuscript.

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### Tables

The basic information of cases and controls

| Variables                  | Case (n=313) | Control (n=508) |   |
|----------------------------|--------------|-----------------|---|
| Age                        | 60.05 ± 6.48 | 71.80 ± 10.09   | <0.001* |
| Sex                        |              |                 | 0.003* |
| Male                       | 238          | 337             |   |
| Female                     | 75           | 171             |   |
| Smoking status             |              |                 | 0.082 |
| Yes                        | 147          | 216             |   |
| No                         | 164          | 292             |   |
| BMI                        | 24.67 ± 4.62 | 24.35 ± 4.58    | 0.587 |
| FEV₁ /FVC                  | 0.56 ± 0.05  | 0.79 ± 0.04     |   |

BMI: Body mass index; FEV₁: Forced expiratory volume in 1 second; FVC: Forced vital capacity

*p <0.05 indicates statistical significance

### Table 2

Primers used in this study

| SNP_ID      | 2nd-PCRPR | 1st-PCRPR | UEP_DIR | UEP_SEQ |
|-------------|-----------|-----------|---------|---------|
| rs10509679  | ACGTGATGGTGGAGTGGATCGCTTAGCTGATG | ACGTGATGGTGGGTATAAATGATGATCGCTGATG | F | tagcGAGTGAAG |
| rs1934967   | ACGTGATGGTGGTGGACTCTCGTACTGATG | ACGTGATGGTGGTGGCTACCCCTGCCAGAAATCCACGAGA | F | TTAGTGTGCTAAGAA |
| rs1934968   | ACGTGATGGTGGTGGACTCTCGTACTGATG | ACGTGATGGTGGTGGCTACCCCTGCCAGAAATCCACGAGA | F | TTAGTGTGCTAAGAA |
| rs9332220   | ACGTGATGGTGGTGGACTCTCGTACTGATG | ACGTGATGGTGGTGGCTACCCCTGCCAGAAATCCACGAGA | F | TTAGTGTGCTAAGAA |
| rs75665761  | ACGTGATGGTGGTGGACTCTCGTACTGATG | ACGTGATGGTGGTGGCTACCCCTGCCAGAAATCCACGAGA | F | TTAGTGTGCTAAGAA |
| rs4494250   | ACGTGATGGTGGTGGACTCTCGTACTGATG | ACGTGATGGTGGTGGCTACCCCTGCCAGAAATCCACGAGA | F | TTAGTGTGCTAAGAA |
| rs75665761  | ACGTGATGGTGGTGGACTCTCGTACTGATG | ACGTGATGGTGGTGGCTACCCCTGCCAGAAATCCACGAGA | F | TTAGTGTGCTAAGAA |

* p <0.05 indicates statistical significance
Table 3

Basic information of candidate SNPs in this study

| SNP            | Chr | Gene     | Position   | Allele A/B | HWE p value | OR (95% CI)     | p   |
|----------------|-----|----------|------------|------------|-------------|-----------------|-----|
| rs10509679     | 10  | CYP2C9   | 94948469   | A/G        | 1.000       | 0.89 (0.72 - 1.12) | 0.321 |
| rs1934967      | 10  | CYP2C9   | 94981669   | T/C        | 1.000       | 1.16 (0.90 - 1.50)    | 0.250 |
| rs1934968      | 10  | CYP2C9   | 94982060   | A/G        | 1.000       | 0.98 (0.80 - 1.22)    | 0.884 |
| rs9332220      | 10  | CYP2C9   | 94984186   | A/G        | 0.433       | 0.64 (0.43 - 0.94)    | 0.021*|
| rs111853758    | 10  | CYP2C19  | 94793932   | G/T        | 0.138       | 0.65 (0.45 - 0.96)    | 0.027*|
| rs4494250      | 10  | CYP2C19  | 94804000   | A/G        | 0.467       | 1.05 (0.81 - 1.35)    | 0.714 |
| rs75665761     | 10  | CYP2C19  | 94806855   | A/G        | 0.709       | 1.31 (0.89 - 1.93)    | 0.176 |

SNP: single nucleotide polymorphisms; Chr: Chromosome; HWE: Hardy-Weinberg equilibrium; OR: odds ratio; 95% CI: 95% confidential interval

*p <0.05 indicates statistical significance

Table 4

Genotype frequencies of the SNPs and their associations with risk of COPD

| SNP            | Gene     | Model | Genotype | Case | Control | OR (95% CI)     | p   |
|----------------|----------|-------|----------|------|---------|-----------------|-----|
| rs1934968      | CYP2C9   | genotype | GG      | 96   | 186     | 1               |     |
|                |          |        | AG      | 152  | 240     | 1.15 (0.77 - 1.71) | 0.500 |
|                |          |        | AA      | 33   | 77      | 0.59 (0.31 - 1.09) | 0.092 |
|                |          | dominant | GG      | 96   | 186     | 1               |     |
|                |          |        | AG+AA   | 185  | 317     | 1.01 (0.69 - 1.47) | 0.980 |
|                |          | recessive | GG+AG  | 248  | 426     | 1               |     |
|                |          |        | AA      | 33   | 77      | 0.54 (0.30 - 0.96) | 0.037*|
|                |          | additive | —      | —    | —       | 0.86 (0.65 - 1.14) | 0.295 |

OR: odds ratio; 95% CI: 95% confidential interval

*p <0.05 indicates statistical significance

Table 5

The association between SNPs and COPD under gender stratification analysis

| SNP            | Gene     | Allele | Male Case | Male Control | Male OR (95% CI) | p   | Female Case | Female Control | Female OR (95% CI) | p   |
|----------------|----------|--------|-----------|--------------|-----------------|-----|--------------|------------------|----------------------|-----|
| rs9332220      | CYP2C9   | G      | 447       | 607          | 1               |     | 140          | 313              | 0.97 (0.37 - 1.63)   | 1   |
|                |          | A      | 29        | 67           | 0.59 (0.37 - 0.92) | 0.020*| 10           | 29               | 0.77 (0.37 - 1.63)   | 0.493 |
| rs111853758    | CYP2C19  | T      | 418       | 602          | 1               |     | 136          | 311              | 1.05 (0.81 - 1.35)   | 0.714 |
|                |          | G      | 30        | 70           | 0.62 (0.40 - 0.96) | 0.032*| 10           | 31               | 0.74 (0.35 - 1.55)   | 0.419 |
OR: odds ratio; 95% CI: 95% confidential interval

*p <0.05 indicates statistical significance