GENETIC POLYMORPHISM OF MATRIX METALLOPROTEINASE 9 AND SUSCEPTIBILITY TO CHRONIC OBSTRUCTIVE PULMONARY DISEASE: A META-ANALYSIS

GENETSKI POLIMORFIZAM MATRIKS METALOPROTEINAZE 9 I OSETLJIVOST NA OPSTRUKTIVNU BOLEST PLUĆA: META ANALIZA

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Summary

Background: To systematically analyze the influence of genetic polymorphisms of matrix metalloproteinase 9 (MMP9) on susceptibility to chronic obstructive pulmonary disease (COPD).

Methods: Relevant literatures reporting MMP9 and susceptibility to COPD in PubMed, Web of Science, VIP, Wanfang and CNKI databases were searched using the key words »matrix metalloproteinases 9/MMP9, COPD/chronic obstructive pulmonary disease«. Data of eligible literatures were extracted and analyzed for the odds ratio (OR) and corresponding 95% CI.

Results: A total of 16 independent studies reporting MMP9-1562C/T and COPD patients were enrolled and analyzed. None of the genetic models revealed the relationship between MMP9-1562C/T and susceptibility to COPD. Subgroup analyses identified lower risk of COPD in Chinese population carrying the TT genotype for the MMP-9 rs3918242 relative to those carrying CT and CC genotypes (P=0.03, OR=0.67, 95% CI=0.46–0.97).

Conclusions: Chinese population carrying the TT genotype for the MMP-9 rs3918242 present lower susceptibility to COPD relative to those carrying CT and CC genotypes.

Keywords: MMP9, polymorphism, COPD, meta-analysis

Kratak sadržaj

Uvod: Sistematska analiza uticaja genetskih polimorfizama matriks metaloproteinaze 9 (MMP9) na osetljivost hronične opstruktivne bolesti pluća (HOBP).

Metode: Relevantna literatura koja izveštava o MMP9 i podložnosti HOBP u bazama podataka PubMed, Web of Science, VIP, Wanfang i CNKI pretravljena je korišćenjem ključnih reči »matriks metaloproteinaze 9/MMP9, COPD/hronična opstruktivna bolest pluća«. Podaci iz kvalifikovane literature su ekstrahovani i analizirani za odnos šanse (OR) i odgovarajući 95% CI.

Rezultati: Ukupno je uključeno i analizirano 16 nezavisnih studija koje su izveštavale o pacijentima sa MMP9-1562C/T i HOBP. Nijedan od genetskih modela nije otkrio vezu između MMP9-1562C/T i osetljivosti na HOBP. Analize podgrupa identificirale su niži rizik od HOBP kod kineske populacije koja nosi TT genotip za MMP-9 rs3918242 u odnosu na one koji nose CT i CC genotipove (P=0.03, OR=0.67, 95% CI=0.46–0.97).

Zaključak: Kineska populacija koja nosi TT genotip za MMP-9 rs3918242 predstavlja manju osetljivost na HOBP u odnosu na one sa CT i CC genotipovima.

Ključne reči: MMP9, polimorfizam, HOBP, meta-analiza

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Introduction

Chronic obstructive pulmonary disease (COPD) is a worldwide disease affecting approximately 3 million people. It is estimated that COPD will be the third leading cause of death by 2020 (1). As a chronic airway inflammatory disease, COPD is characterized by incomplete reversible airflow limitation, inflammatory cell infiltration, excessive mucus secretion, and airway remodeling (2). The precise molecular mechanism underlying the pathogenesis of COPD remains unclear. At present, it is generally believed that several risk factors are directly related to the pathogenesis of COPD, including host and environmental factors (3). Among environmental factors, smoking, exposure to chemicals, indoor and outdoor air pollution are risk factors for COPD (4). Host factors of COPD include antitrypsin-1, excessive deposition of extracellular matrix (ECM), corticosteroids, inflammatory stimuli, and metabolic imbalances (5, 6).

Matrix metalloproteinases (MMPs) are members of the metformin group and they are capable of degrading ECMs and regulating extracellular signaling networks (7). MMPs are important in COPD. They degrade matrix proteins (elastin, collagen) during the disease progression (8). In the past decade, abundant researches have been conducted to analyze the relationship between single nucleotide polymorphisms (SNPs) of MMPs and COPD risk in some populations (9–12). However, the conclusions were controversial. Some reports demonstrated the certain influence of MMPs on the occurrence of COPD (13–18), while others did not (9, 12, 19, 20). These conflicting findings may be explained by limited sample size, false positive results, and publication bias. In this paper, we performed a comprehensive meta-analysis to assess the influence of MMP polymorphisms on COPD.

Materials and Methods

Search strategy of literatures

Relevant literatures reporting the relationship between polymorphisms of MMP9-1562C/T and susceptibility to COPD in PubMed, Web of Science, VIP, Wanfang and CNKI databases were searched using the key words »matrix metalloproteinases 9/MMP9, COPD/chronic obstructive pulmonary disease«. There were no limitations on published languages. Citations in each literature were manually reviewed.

Inclusive and exclusive criteria

Inclusive criteria were as follows: 1) Case-control studies conducted in humans; 2) Literatures published complete data or raw data that could calculate the genotype distribution; 3) COPD patients underwent diagnosis of pulmonary function index; 4) Literatures were conducted on the influence of polymorphisms of MMP9-1562C/T on susceptibility to COPD.

Exclusive criteria were as follows: 1) Repeated literatures; 2) Literatures lacked valid raw data; 3) Reviews, comments, animal experiments, researches on mechanism and case reports; 4) The latest studies or those with a larger sample size were selected if data overlapping; 5) Unpublished data.

Flow diagram of literature searching was depicted in Figure 1.

Data extraction

Data were independently extracted and analyzed by two researchers, and the third one was responsible for solving any disagreement. Extracted data included: 1) Baseline data of literatures, including publication origin, first author, year or publication, and etc.; 2) Basic characteristics of subjects, including sample size, research country, genotype number and distribution, HWE in control group and etc.

Statistical analysis

Heterogeneity test was conducted by calculating odds ratio (OR) and the corresponding 95% CI with the $I^2$ test and the Q test. The pooled OR in studies lacking the heterogeneity was calculated by the fix-effects model. Otherwise, a random-effects model was used. Sensitivity analysis was performed by removing one study each time and analyzing the remaining in a combination way. The HWE of control genotype distribution was evaluated using the $\chi^2$ test and $P<0.05$ considered as inequivalent. Publication bias was evaluated by depicting funnel plots and quantified by Egger’s test. Data analyses were carried out using RevMan 5.3 and STATA12.0.

Figure 1 Flow diagram of the publication selection process.
Results

Baseline characteristics of eligible literatures

Initially, 157 literatures in PubMed, 151 in Web of Science, 1 in CNKI, 77 in VIP and 15 in Wanfang database were searched out, with a total of 395 literatures. A total of 62 replicates and 287 irrelevant literatures were excluded after the first-round screening. Subsequently, 14 literatures on mechanisms, 6 reviews, 6 literatures reporting other diseases, 2 literatures without complete data and 2 reporting other mutant sites were excluded. Finally, 16 literatures were included in this study (Figure 1).

Table I Main characteristics of studies included in the meta-analysis.

| Author          | Year | Country | Journal name/publication origin | Genotyping methods | SNP loci (pHWE) | Sample size | Control | Sample |
|-----------------|------|---------|---------------------------------|-------------------|----------------|-------------|---------|--------|
| Zhou            | 2004 | China   | Chinese Medical Journal         | PCR-sequence      | rs3918242 (pHWE=0.92) | 100 (male=98, female=) | 100 (male=99, female=1) | Whole blood |
| Isao Ito        | 2005 | Japan   | Am J Respir Crit Care Med       | PCR-RFLP          | rs3918242 (pHWE=0.41) | 84 (male=81, female=3) | 85 (male=69, female=16) | Whole blood |
| Zhang Rongbao   | 2005 | China   | Chin J Epidemiol                | PCR-RFLP          | rs3918242 (pHWE=0.09) | 147 (male=135, female=12) | 120 (male=110, female=10) | Whole blood |
| Han             | 2006 | Asian   | Chin J Tuberc Respir Dis        | PCR-RFLP          | rs3918242 (pHWE=0.48) | 60 | 52 | Whole blood |
| Testaigzi       | 2006 | Caucasian | Int J Chron Obstruct Pulmon Dis | PCR-RFLP      | rs3918242 (pHWE=0.39) | 123 | 262 | Whole blood |
| Korytina        | 2008 | Russia  | Russian Journal of Genetics     | PCR-RFLP          | rs3918242 (pHWE=0.53) | 318 | 319 | Whole blood |
| Shih-Lung Cheng | 2009 | Taiwan (China) | Biochem Genet                  | PCR-RFLP          | rs3918242 (pHWE=0.23) | 184 (male=152, female=32) | 212 (male=182, female=30) | Whole blood |
| H. Schirmer     | 2009 | Brazil  | Genetics and Molecular Research | PCR              | rs3918242 (pHWE=0.60) | 89 | 97 | Whole blood |
| Shih-Yup Lee    | 2010 | Korean  | Basic Science Investigations    | PCR-sequence      | rs3918242 (pHWE=0.376) | 301 | 333 | Whole blood |
| Hua             | 2010 | China   | Int J Respi                     | PCR-RFLP          | rs3918242 (pHWE=0.04) | 180 (male=142, female=38) | 180 (male=130, female=50) | Whole blood |
| Korytina        | 2012 | Russia  | Molecular Biology               | PCR-RFLP          | rs3918242 (pHWE=0.67) | 391 | 514 | Whole blood |
| Sarra Bchir     | 2015 | Tunisia | Mol Diagn Ther                  | PCR-RFLP          | rs3918242 (pHWE=0.02) | 138 (male=122, female=16) | 216 (male=155, female=61) | Whole blood |
| Marja Stankovic | 2016 | Serbia  | Environmental and Molecular Mutagenesis. | PCR-RFLP | rs3918242 (pHWE=0.28) | 86 | 100 | Whole blood |
| Marja Stankovic | 2017 | Serbia  | JOURNAL OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE | PCR-RFLP | rs3918242 (pHWE=0.28) | 122 | 100 | Whole blood |
| Tan Jie         | 2017 | China   | Journal Of Inner Mongolia Medical University | PCR-RFLP | rs3918242 (pHWE<0.001) | 186 (male=92, female=294) | 219 (male=105, female=112) | Whole blood |
| Lwona Gilowska  | 2018 | Poland  | BioMed Research International   | PCR-RFLP          | rs3918242 (pHWE=0.53) | 335 (male=87, female=248) | 309 (male=229, female=80) | Whole blood |

SNP = Single nucleotide polymorphism; HWE = Hardy-Weinberg equilibrium; pHWE = p-value of Hardy-Weinberg Equilibrium test in controls for each locus; PCR = polymerase chain reaction
Baseline characteristics of eligible literatures were listed in Table I. Briefly, 16 case-control studies were published from 2004–2018, including 13 studies published in English-language scientific journals and 3 in Chinese-language scientific journals. Genotyping methods were conducted using polymerase chain reaction (PCR), PCR-RFLP and PCR-sequence. Identification of single nucleotide polymorphisms (SNPs) was conducted by extracting blood samples of subjects.

In the 16 eligible literatures, 5 analyzed Chinese population, 1 analyzed Japanese population, 2 analyzed Russian population, 1 analyzed Korean population, 1 analyzed Tunisian population, 2 analyzed Serbian population, 1 analyzed Poland population, 1 analyzed Asian population and 1 analyzed Caucasian population. Sample size of each literature was 60-391.

Meta-analysis

A total of 2011 COPD patients and 2249 healthy controls were enrolled. The influence of MMP9 (-1562) C/T on susceptibility to COPD was assessed using different genetic models. No relationship was found between the CC vs. TT genotype of MMP9 rs391842 and susceptibility to COPD in the allele model (P=0.41, OR=1.12, 95% CI=0.86–1.47) (Figure 2A-C). The other three genetic models obtained the same conclusion, including the dominant model (CC vs. CT+TT, P=0.13, OR=0.82, 95% CI=0.63–1.06), recessive model (TT vs. CC+CT, P=0.87, OR=0.97, 95% CI=0.65–1.43) and over-dominant model (CT vs. CC+TT, P=0.51, OR=1.13, 95% CI=0.79–1.61).

Subgroup analyses were performed based on the ethnic populations, involving Asian population (8 literatures), European population (3 literatures), Caucasian population (3 literatures) and African population (2 literatures). The random-effects model was utilized owing to the different degrees of hetero-

![Figure 2A](Image) Forest map of the relationship between the SNP of MMP-9 rs3918242 and susceptibility to COPD.
Figure 2B Forest map of the relationship between the SNP of MMP-9 rs3918242 and susceptibility to COPD.
geneity ($I^2>50\%$, $P<0.05$). The data showed no relationship between MMP9 polymorphisms and COPD risk under the different genetic models ($P>0.05$) (Figure 3 C-D).

Subsequently, we individually analyzed the relationship between MMP9 polymorphisms and COPD in Chinese population, involving 5 literatures (15, 18, 21–23). Except for the recessive model (TT vs. CC&CT) analyzed by the fix-effects model ($P=0.13$, $I^2=46\%$), the remaining were assessed using the random-effects model ($I^2>50\%$, $P<0.05$) (Figure 4). Our data showed that Chinese population carrying the TT genotype for the MMP-9 rs3918242 was closely related to susceptibility to COPD relative to those carrying CT and CC genotypes ($P=0.03$, OR=0.67, 95% CI=0.46–0.97). Such a difference was not observed in the dominant model (CC vs. CT&TT), over-dominant model (CT vs. CC&TT) and allele model (C Allele vs. T Allele) ($P>0.05$) (Figure 4).

**Heterogeneity and sensitivity analysis**

Significant heterogeneity was identified in the dominant model, over-dominant model and allele model analyzing the relationship between MMP9 (-1562) C/T and susceptibility to COPD (all $P<0.001$). No remarkable changes in $I^2$ and $P$ values were observed after removing a single study. In addition, sensitivity analysis was not altered by removing any study each time (data not shown).

In the subgroup analyses based on different ethnic populations, all genetic models showed the results of $I^2>50\%$ and $P<0.05$. We did not find any changes in $I^2$ and $P$ values after removing a single study. Sensitivity analysis was not influenced by removing a single study (data not shown).
Figure 3A, B Subgroup analyses of the relationship between the SNP of MMP-9 rs3918242 and susceptibility to COPD in different regions and different pairs of comparisons.
Figure 3C, D Subgroup analyses of the relationship between the SNP of MMP-9 rs3918242 and susceptibility to COPD in different regions and different pairs of comparisons.
Publication bias

A wide range of search strategies was carried out to minimize potential publication biases. After quantification using Egger’s test, the data showed no publication biases between MMP9 (-1562) C/T and susceptibility to COPD in the three genetic models except for the allele model (CC vs. CT+TT, P=0.325; TT vs. CC+CT, P=0.541; CT vs. CC&T, P=0.553; C allele vs. T allele, P=0.017) (Figure 5).

|                  | Study or Subgroup | Experimental Events | Control Events | Total Events | Weight | Odds Ratio M-H. Random 95% CI | Odds Ratio M-H. Fixed 95% CI |
|------------------|-------------------|---------------------|----------------|-------------|--------|-----------------------------|------------------------------|
| **CC vs. CT&TT** | Hua 2010          | 120                 | 162            | 282         | 6.04   | 0.22 [0.12, 0.40]            |                              |
|                  | Shin-Yup Lee 2009 | 534                 | 226            | 760         | 16.5   | 0.76 [0.62, 0.82]            |                              |
|                  | TAN Jie 2017      | 93                  | 67             | 160         | 1.31   | 0.48 [0.32, 0.71]            |                              |
|                  | ZHANG Rong-bao 2005 | 106             | 120            | 226         | 0.58   | 0.52 [0.37, 0.72]            |                              |
|                  | Zhou 2004         | 86                  | 98             | 184         | 0.13   | 0.13 [0.03, 0.57]            |                              |
| **Total (95% CI)** | 947               | 919                | 1866          | 1.68       | 0.59 [0.26, 1.34]            |                              |
| **TT vs. CC&CT** | Hua 2010          | 0                   | 2              | 2           | 0.37   | 0.20 [0.01, 4.15]            |                              |
|                  | Shin-Yup Lee 2009 | 1                   | 9              | 10          | 0.12   | 0.12 [0.02, 0.65]            |                              |
|                  | TAN Jie 2017      | 78                  | 76             | 154         | 0.82   | 0.82 [0.55, 1.22]            |                              |
|                  | ZHANG Rong-bao 2005 | 0              | 3              | 3           | 0.11   | 0.11 [0.01, 2.23]            |                              |
|                  | Zhou 2004         | 0                   | 100            | 100         | Not estimate                     |                              |
| **Total (95% CI)** | 947               | 919                | 1866          | 1.68       | 0.67 [0.46, 0.97]            |                              |
| **CT vs. CC&TT** | Hua 2010          | 60                  | 16             | 76          | 5.13   | 0.93 [0.81, 1.05]            |                              |
|                  | Shin-Yup Lee 2009 | 59                  | 81             | 140         | 0.76   | 0.52 [0.37, 0.74]            |                              |
|                  | TAN Jie 2017      | 14                  | 76             | 90          | 0.10   | 0.10 [0.05, 0.18]            |                              |
|                  | ZHANG Rong-bao 2005 | 41              | 120            | 161         | 2.06   | 2.06 [1.12, 3.78]            |                              |
|                  | Zhou 2004         | 14                  | 2              | 16          | 0.79   | 0.79 [0.46, 1.37]            |                              |
| **Total (95% CI)** | 947               | 919                | 1866          | 1.68       | 1.35 [0.35, 5.25]            |                              |
| **C Allele vs. T Allele** | Hua 2010 | 60                  | 20             | 80          | 3.40   | 3.40 [2.00, 5.77]            |                              |
|                  | Shin-Yup Lee 2009 | 61                  | 99             | 160         | 0.85   | 0.85 [0.48, 1.49]            |                              |
|                  | TAN Jie 2017      | 172                 | 372            | 544         | 0.41   | 0.41 [0.31, 0.55]            |                              |
|                  | ZHANG Rong-bao 2005 | 41              | 240            | 281         | 1.39   | 1.39 [0.82, 2.37]            |                              |
|                  | Zhou 2004         | 14                  | 2              | 16          | 0.75   | 0.75 [0.46, 1.26]            |                              |
| **Total (95% CI)** | 1894              | 1838               | 3732          | 3.17       | 1.35 [0.93, 1.95]            |                              |

*Figure 4* Subgroup analyses of the relationship between the SNP of MMP-9 rs3918242 and susceptibility to COPD in Chinese population and different pairs of comparisons.
Discussion

MMPs are a class of zinc-dependent endopeptidases that degrade major protein components of the ECM. They participate in development- and inflammation-related tissue remodeling and repair (7). MMP-9 (gelatinase B) can degrade ECM proteins, such as type IV collagen and gelatin (24). In addition, it exerts a vital role in airway inflammation and remodeling (25, 26). MMP-9 protects ventilator-induced lung injury by reducing infiltration of alveolar neutrophils (27).

COPD is a common respiratory disease characterized by airflow limitation. The pathogenesis of COPD is complex, involving inflammatory response, oxidant-antioxidant imbalance, and MMPs-induced proteolysis of the alveolar wall. MMP9, one of the most widely studied MMPs, decomposes most of the components of ECM by degrading structural proteins, such as collagen and elastin (28). Many studies have reported the involvement of MMP9 in the development of lung diseases (29). MMP9 polymorphism is identified to increase the susceptibility to respiratory diseases (30–33). Multiple SNPs of MMP9 have been discovered. Among them, C/T mutation on MMP9 (-1562) rs3918242 results in the increased promoter activity owing to the deletion of the transcriptional repressor binding site (34).

So far, studies focusing on the correlation between MMP9 -1562 C/T polymorphism and COPD are relatively rare and uncertain. Studies with a small sample size lack the statistical power and often lead to contradictory conclusions. Meta-analysis provides convincing evidences by calculating data extracted from multiple studies. In this paper, we obtained the conclusion that MMP9 -1562 C/T polymorphism was not associated with susceptibility to COPD in different putative genetic models. Subgroup analyses showed that Chinese population carrying the TT genotype for the MMP9 rs3918242 are risky of COPD relative to those carrying CT and CC genotypes.

Inconsistent with our results, some studies have demonstrated that the MMP9 -1562 C>T polymorphism indeed influences COPD risk. Zhou et al. (35) illustrated that the TT genotype of MMP9 -1562 C/T polymorphism is a genetic risk factor for severe COPD. Korytina et al. (36) have indicated the correlation between the TT genotype of MMP9 -1562 C/T polymorphism and COPD severity. Similarly, a study conducted in Russia showed a significant difference in the frequency distribution of MMP9 -1562 C>T
among COPD patients with different severity levels (37).

Some shortcomings in this study should be pointed out. First of all, many complex factors were not adjusted, such as gender, age, and smoking history. Secondly, some studies (16, 20, 23) had small sample sizes and did not have enough capacity to detect the risk of COPD. Thirdly, the lack of raw data limited the further analysis of the potential interactions between genetic risks and environmental factors in COPD. Studies with large sample sizes in a multicenter hospital are required for further validation.

**Conclusions**

Chinese population carrying the TT genotype for the MMP-9 rs3918242 present lower susceptibility to COPD relative to those carrying CT and CC genotypes.

**Acknowledgements.** No.

**Financial Disclosure.** This study was supported by the Key Project of Qingdao 2020 Traditional Chinese Medicine Scientific Research Plan (No: 2020-zyz002) and Shandong Traditional Chinese Medicine Science and Technology Project (No: 2020M108).

**Conflict of interest statement**

All the authors declare that they have no conflict of interest in this work.

**References**

1. Singh S, Loke YK, Enright PL, Furberg CD. Mortality associated with tiotropium mist inhaler in patients with chronic obstructive pulmonary disease: systematic review and meta-analysis of randomised controlled trials. BMJ 2011; 342: d5215.
2. Rabe KF, Watz H. Chronic obstructive pulmonary disease. Lancet 2017; 389(10082): 1931–40.
3. Brusselle GG, Joos GF, Bracke KR. New insights into the immunology of chronic obstructive pulmonary disease. Lancet 2011; 378(9795): 1015–26.
4. Clancy J, Nobes M. Chronic obstructive pulmonary disease: nature-nurture interactions. Br J Nurs 2012; 21(13): 772–81.
5. Yun CM, Sang XY. Role of proteinase-activated receptor-1 gene polymorphisms in susceptibility to chronic obstructive pulmonary disease. Genet Mol Res 2015; 14(4): 13215–20.
6. Gan WQ, FitzGerald JM, Carlsten C, Sadatsafavi M, Brauer M. Associations of ambient air pollution with chronic obstructive pulmonary disease hospitalization and mortality. Am J Respir Crit Care Med 2013; 187(7): 721–7.
7. Churg A, Zhou S, Wright JL. Series »matrix metalloproteinases in lung health and disease«: Matrix metalloproteinases in COPD. Eur Respir J 2012; 39(1): 197–209.
8. Ishii T, Abboud RT, Wallace AM, English JC, Coxson HO, Finley RJ, et al. Alveolar macrophage proteinase/antiproteinase expression in lung function and emphysema. Eur Respir J 2014; 43(1): 82–91.
9. Cheng SL, Yu CJ, Yang PC. Genetic polymorphisms of cytochrome p450 and matrix metalloproteinase in chronic obstructive pulmonary disease. Biochem Genet 2009; 47(7–8): 591–601.
10. van Diemen CC, Postma DS, Aulchenko YS, Snijders PJ, Oostra BA, van Duijn CM, et al. Novel strategy to identify genetic risk factors for COPD relative to those carrying CT and CC genotypes.

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1. Singh S, Loke YK, Enright PL, Furberg CD. Mortality associated with tiotropium mist inhaler in patients with chronic obstructive pulmonary disease: systematic review and meta-analysis of randomised controlled trials. BMJ 2011; 342: d5215.
2. Rabe KF, Watz H. Chronic obstructive pulmonary disease. Lancet 2017; 389(10082): 1931–40.
3. Brusselle GG, Joos GF, Bracke KR. New insights into the immunology of chronic obstructive pulmonary disease. Lancet 2011; 378(9795): 1015–26.
4. Clancy J, Nobes M. Chronic obstructive pulmonary disease: nature-nurture interactions. Br J Nurs 2012; 21(13): 772–81.
5. Yun CM, Sang XY. Role of proteinase-activated receptor-1 gene polymorphisms in susceptibility to chronic obstructive pulmonary disease. Genet Mol Res 2015; 14(4): 13215–20.
6. Gan WQ, FitzGerald JM, Carlsten C, Sadatsafavi M, Brauer M. Associations of ambient air pollution with chronic obstructive pulmonary disease hospitalization and mortality. Am J Respir Crit Care Med 2013; 187(7): 721–7.
7. Churg A, Zhou S, Wright JL. Series »matrix metalloproteinases in lung health and disease«: Matrix metalloproteinases in COPD. Eur Respir J 2012; 39(1): 197–209.
8. Ishii T, Abboud RT, Wallace AM, English JC, Coxson HO, Finley RJ, et al. Alveolar macrophage proteinase/antiproteinase expression in lung function and emphysema. Eur Respir J 2014; 43(1): 82–91.
9. Cheng SL, Yu CJ, Yang PC. Genetic polymorphisms of cytochrome p450 and matrix metalloproteinase in chronic obstructive pulmonary disease. Biochem Genet 2009; 47(7–8): 591–601.
10. van Diemen CC, Postma DS, Aulchenko YS, Snijders PJ, Oostra BA, van Duijn CM, et al. Novel strategy to identify genetic risk factors for COPD relative to those carrying CT and CC genotypes.

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9 are a risk factor for COPD. Int J Chron Obstruct Pulmon Dis 2006; 1(3): 267–78.

18. Zhou M, Huang SG, Wan HY, Li B, Deng WW, Li M. Genetic polymorphism in matrix metalloproteinase-9 and the susceptibility to chronic obstructive pulmonary disease in Han population of south China. Chin Med J (Engl) 2004; 117(10): 1481–4.

19. Haq I, Chappell S, Johnson SR, Lotya J, Daly L, Morgan K, et al. Association of MMP-2 polymorphisms with severe and very severe COPD: a case control study of MMPs-1, 9 and 12 in a European population. BMC Med Genet 2010; 11: 7.

20. Ito I, Nagai S, Handa T, Muro S, Hirai T, Muro S, et al. Matrix metalloproteinase-9 promoter polymorphism associated with upper lung dominant emphysema. Am J Respir Crit Care Med 2005; 172(11): 1378–82.

21. Hua DM, Ding LY, Wang Z, Lv FZ, Xiao JL, Chi P, Zhuo JM. Study on Genetic Polymorphism of Matrix Metalloproteinase 9 and Susceptibility to Chronic Obstructive Pulmonary Disease in Tibet. Int J Respi 2010; 30: 1157–60.

22. Tan J, Bai YF, Sun C, Xu XX. Study on Genetic Polymorphism of MMP-9 and Susceptibility to COPD in Inner Mongolia. Journal of Inner Mongolia Medical University 2017; 39: 50–3, 59.

23. Zhang RB, He QY, Yang RH, Lu BB, Liu YJ. Study on Genetic Polymorphism of Matrix Metalloproteinase 1, 9, 12 and Susceptibility to Chronic Obstructive Pulmonary Disease among Han Chinese in Northern China. Chin J Epidemiol 2005; 26: 907–10.

24. Newby AC. Dual role of matrix metalloproteinases (matrixins) in intimal thickening and atherosclerotic plaque rupture. Physiol Rev 2005; 85(1): 1–51.

25. Kumar M, Phougat N, Ruhil S, Dhankhar S, Balhara M, Chhillar AK. Genomics of Chronic Obstructive Pulmonary Disease (COPD); Exploring the SNPs of Protease-Antiprotease Pathway. Curr Genomics 2013; 14(3): 204–13.

26. Renckens R, Roelofs JJ, Florquin S, de Vos AF, Lijnen HR, van’t VC, et al. Matrix metalloproteinase-9 deficiency impairs host defense against abdominal sepsis. J Immunol 2006; 176(6): 3735–41.

27. Albaiceta GM, Gutierrez-Fernandez A, Parra D, Astudillo A, Garcia-Prieto E, Taboada F, et al. Lack of matrix metalloproteinase-9 worsens ventilator-induced lung injury. Am J Physiol Lung Cell Mol Physiol 2008; 294(3): L535–43.

28. Opdenakker G, Van den Steen PE, Dubois B, Nelissen J, Van Coillie E, Masure S, et al. Gelatinase B functions as regulator and effector in leukocyte biology. J Leukoc Biol 2001; 69(6): 851–9.

29. Öner Ö, Deyeci F, Telo S, Kuluözürt M, Balin M. MR-proADM and MR-proANP levels in patients with acute pulmonary embolism J Med Biochem 2020; 39(3): 328–35.

30. Xu L, Bian W, Gu XH, Shen C. Genetic polymorphism in matrix metalloproteinase-9 and transforming growth factor-beta1 and susceptibility to combined pulmonary fibrosis and emphysema in a Chinese population. Kaohsiung J Med Sci 2017; 33(3): 124–9.

31. Liu JW, Chen DQ. Correlations of MMP-2 and MMP-9 gene polymorphisms with the risk of hepatopulmonary syndrome in cirrhotic patients: A case-control study. Kaohsiung J Med Sci 2018; 34(11): 634–42.

32. Jiang S, Yang ZH, Chen YY, He Z, Zhou Y, Gao Y, et al. MMP-9 genetic polymorphism may confer susceptibility to COPD. Genet Mol Res 2016; 15(2): gmr.15026272.

33. Zhang HT, Fang SC, Wang CY, Wang W, Wu J, Wang C, et al. MMP-9 1562C>T; T Gene Polymorphism and Efficacy of Glucocorticoid Therapy in Idiopathic Pulmonary Fibrosis Patients. Genet Test Mol Biomarkers 2015; 19(11): 591–7.

34. Zhang B, Ye S, Herrmann SM, Eriksen P, de Maat M, Evans A, et al. Functional polymorphism in the regulatory region of gelatinase B gene in relation to severity of coronary atherosclerosis. Circulation 1999; 99(14): 1788–94.

35. Zhou H, Wu Y, Jin Y, Zhou J, Zhang C, Che L, et al. Genetic polymorphism of matrix metalloproteinase family and chronic obstructive pulmonary disease susceptibility: a meta-analysis. Sci Rep 2013; 3: 2818.

36. Korytina GF, Tselousova OS, Akhmadishina LZ, Victorova EV, Zagidullin S, Victorova TV. Association of the MMP3, MMP9, ADAM33 and TIMP3 genes polymorphic markers with development and progression of chronic obstructive pulmonary disease. Mol Biol (Mosk) 2012; 46(3): 487–99.

37. Korytina GF, Akhmadishina LZ, Ianaeva DG, Viktorova TV. Polymorphism in promoter regions of matrix metalloproteinases (MMP1, MMP9, and MMP12) in chronic obstructive pulmonary disease patients. Genetika 2008; 44(2): 242–9.

Received: September 28, 2021
Accepted: December 14, 2021