Genetic variation in PTX3 is associated with susceptibility to community-acquired pneumonia in adults: a retrospective case control study

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Research

Keywords: Community-acquired pneumonia, innate immunity, Pentraxin 3, single nucleotide polymorphisms

Posted Date: July 8th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-40415/v1

Abstract

Background

Evidence indicates that single nucleoid polymorphisms (SNPs) of key molecules in innate immunity are related to clinical outcome of community-acquired pneumonia (CAP). Pentraxin 3 (PTX3) is a member of the acute-phase reactants superfamily and plays an important role against various diseases. The purpose of the current study was to assess the association between PTX 3 SNP and the risk of CAP.

Methods

This is a retrospective case-control study. Patients who were diagnosed with CAP between January 2018 to December 2019 in the Department of Pulmonary and Critical Care Medicine at Sun Yat-sen Memorial Hospital were included as CAP group. Then CAP cases were matched 1:1 by gender with non-infectious hospitalized patients during the same time. We detected the genotypes, allele frequencies and haplotype distributions of three SNPs within PTX3 gene (rs2305619, rs3816527, and rs1840680) by polymerase chain reaction sequencing in CAP group and control group, and compared their associations with the risk of CAP.

Results

Three SNPs in both groups were consist with Hardy-Weinberg equilibrium. A strong linkage disequilibrium was detected between any pair of rs2305619, rs3816527 and rs1840680 (|D'|≥0.85). There were no differences of rs2305619 and rs3816527 in genotypic distribution and haplotype frequency between CAP group and control group. However, we identified that SNP rs1840680 AA homozygote was associated with a lower risk of CAP in adults (OR, 0.32; 95% CI, 0.11-0.91; p = 0.03).

Conclusions

Our findings suggested that PTX3 single nucleoid polymorphism was associated with the risk of CAP in adults.

Background

As a common and deadly condition, community-acquired pneumonia (CAP) is increasingly prevalent and remains a significant health problem. Most patients can be cured after antimicrobial treatment,but some individuals may develop acute lung injury and even die from septic shock after rapid disease progression [1]. In America, 77% of CAP hospitalized patients improved, 20% didn't change, and 3% had worsened. Mortality at 30 days was 6% for those who improved, 34% for those who failed, and 34% for those with non-resolving pneumonia. Mortality at 1 year was 23%, 52%, and 51% [2]. In recent years, reports have shown that genetic factors have a certain influence on the susceptibility to infection with pathogens. It has been found that gene polymorphisms of tumor necrosis factor receptor (TNFR), interleukin-1 (IL-1),

interferon regulatory factor-5(IRF-5) and other key molecules in the inflammatory response pathway may be related to the susceptibility, severity and prognosis of CAP [3–7].

Pentraxin-3 (PTX3), a member of the family of long pentraxins, is an acute phase reactive protein. As a key player in innate immunity and inflammation, PTX3 is critical to host defense against microbial infection including bacteria, fungi and viruses [8]. Differing from short-chain pentameric factors mainly derived from the liver such as C-reactive protein (CRP), PTX3 is a marker for systemic inflammation which is produced rapidly by various cells under inflammatory or stress conditions [9]. Serum PTX3 is found to be present at low levels in health status, and significantly increase in patients who suffer from infectious diseases or tissue injury. Some studies suggested that compared with other biomarkers such as CRP, the concentration of PTX3 in serum can deliver better reflection of the inflammatory status, early assessment of disease severity and prediction of prognosis [10–11].

The human PTX3 gene, localizing on human chromosome 3 band q25, is organized in three exons separated by two introns [8]. Three single nucleotide polymorphisms (SNPs) in PTX3 (rs2305619, rs3816527 and rs1840680) have been demonstrated functional significance. Previous studies have found that PTX3 gene polymorphisms are associated with several Infectious diseases, such as tuberculosis in West Africans, *Pseudomonas aeruginosa* in patients with pulmonary cystic fibrosis, and invasive aspergillosis in patients with chronic obstructive pulmonary disease (COPD) or after hematopoietic stem cell transplantation [12–15].

However, the association between PTX3 genetic variation and the susceptibility to community-acquired pneumonia is still unknown. Therefore, the aim of the present study was to assess the association between three PTX3 SNPs (rs2305619, rs3816527 and rs1840680) and the CAP occurrence.

Methods

We conducted a retrospective case-control study in the Department of Pulmonary and Critical Care Medicine of Sun Yat-sen Memorial Hospital, a university teaching hospital. This study protocol was approved by the Ethics Committees of Sun Yat-sen Memorial Hospital (SYSEC-KY-KS-2020-005). Written informed consent was obtained from each individual that participated in this study or their authorized relatives.

We obtained the medical records of all inpatients in the Department of Pulmonary and Critical Care Medicine of Sun Yat-sen Memorial Hospital from January 2018 and December 2019. A total of 178 participants were enrolled in the present study. Among them, 88 cases were diagnosed with community-acquired pneumonia according to the Chinese Thoracic Society (CTS) guideline [16] and defined as CAP group, while the remaining 90 cases were gender-matched controls without infectious diseases and defined as control group. Exclusion criteria were as follows: (1) age less than 18year; (2) evidence that strongly indicates the presence of active tuberculosis or pulmonary fungal diseases; (3) a history of malignancies undergoing chemotherapy; (3) a documentary medication of long-term corticosteroids or immunosuppressive agents; and (4) a history of acquired immune deficiency syndrome.

Based on the previous study [12–15], we chose three single nucleotide polymorphisms (SNPs; rs2305619, rs3816527, and rs1840680) of PTX3. Genomic DNA was extracted from patient peripheral blood by a DNA extraction kit (Shanghai Generay Biotech, China). The primers and MGB probes (Sango Biotech, Shanghai, China) were designed in Beacon Designer software based on the SNP sequences in National Center for Biotechnology Information (NCBI) SNP database. Then real-time polymerase chain reaction (PCR) was conducted via TaKaRa Premix Ex Taq II Kit (TaKaRa Bio INC). According to the fluorescent color of probes melting curve analysis was used to define the genotyping of SNP and further analyzed by CFX Manager Software 1.6 software (Bio-Rad).

Statistical analysis was performed using SPSS20.0. Categorical variables were compared by the chi-squared test or Fisher's exact test when appropriate. Continuous variables were tested for normal distribution using Kolmogorov-Smirnov test. Differences between two groups were assessed by Student's T-test for parametric data and by the Mann Whitney U test for non-parametric data. Comparisons between values of more than two groups were evaluated by one-way analysis of variance (ANOVA) or Kruskal-Wallis test. Correlation between genotype frequencies and CAP risk was assessed by an adjusted odds ratio (OR) with 95% confidence interval (CI). The linkage disequilibrium among selected SNPs was estimated by calculating pairwise D' and r2 statistics using Haploview (version 4.2; www.broad.mit.edu/mpg/haploview/). Haplotype analysis was also performed using this software. A difference was considered statistically significant when a p value < 0.05.

Results

Patient characteristics

The baseline characteristics of the study population are presented in Table 1. No significant differences between the two groups in terms of gender, age and common comorbidities ($p > 0.05$).

Table 1
Baseline characteristics of CAP patients and controls

	CAP(n = 88)	Controls(n = 90)	*p*-value
Sex			0.37
Male	41(46.6)	48(53.3)	
Female	47(53.4)	42(46.7)	
Age, years	58.6 ± 12.9	56.9 ± 12.7	0.39
Comorbidities			
Diabetes	12(13.6)	10(11.1)	0.65
Hypertension	18(20.5)	17(18.9)	0.85
Chronic heart disease	7(8.0)	12(13.3)	0.33
Values are presented as mean ± SD, median (range) or n (%).			
Abbreviation: CAP, community-acquired pneumonia.			

Associations between PTX3 SNPs and risk of CAP

The selected SNPs (rs2305619, rs38716527 and rs1840680) in this study were in Hardy-Weinberg equilibrium as shown in Table 2. The genotype frequency of rs1840680 AA was significantly different between CAP group and control group ($p = 0.03$). We detected a lower risk of CAP in individuals with rs1840680 AA homozygosity (OR = 0.32, 95% CI = 0.11–0.91, $p < 0.05$) (Table 2).

Table 2
Distribution of rs2305619,rs38716527 and rs1840680 SNP genotypes in CAP patients and controls

SNP	Genotype	CAP(n = 88)	Controls(n = 90)	OR (95% CI)	*p*-value
rs2305619	AA	12(13.6)	18(20.0)	0.60(0.25–1.42)	0.24
	AG	36(40.9)	36(40.0)	0.90(0.47–1.72)	0.75
	GG	40(45.5)	36(40.0)	Reference	-
rs3816527	AA	54(61.4)	53(58.9)	1.36(0.29–6.36)	0.70
	AC	31(35.2)	33(36.7)	1.25(0.26–6.05)	0.78
	CC	3(3.4)	4(4.4)	Reference	-
rs1840680	AA	6(6.8)	16(17.8)	0.32(0.11–0.91)	0.03*
	AG	39(44.3)	37(41.1)	0.91(0.48–1.70)	0.76
	GG	43(48.9)	37(41.1)	Reference	-

*Values are presented as n (%). *p < 0.05.*

Abbreviations: SNP, single nucleotide polymorphism; CAP, community-acquired pneumonia; OR, odds ratio; CI, confidence interval.

However, the allele frequencies of rs1840680 did not differ significantly between CAP group and control group ($p > 0.05$) (Table 3). In addition, no difference in genotype or allele frequency for rs2305619 and rs3816527 were observed between the two groups ($p > 0.05$). With respect to rs2305619 and rs3816527, no evidence of association with CAP risk was found (Table 3).

Table 3
Distribution of rs2305619,rs38716527 and rs1840680 SNP allele in CAP patients and controls

SNP	Allele	CAP(n = 88)	Controls(n = 90)	*OR(95% CI)*	*p*-value
rs2305619	A	60(34.1)	72(40)	1.29(0.84–1.98)	0.25
	G	116(65.9)	108(60.0)	Reference	-
rs3816527	A	139(79.0)	139(77.2)	0.90(0.55–1.49)	0.69
	C	37(21.0)	41(22.8)	Reference	-
rs1840680	A	51(29.0)	69(38.3)	1.50(0.98–2.37)	0.06
	G	125(71.0)	111(61.7)	Reference	-

Values are presented as n (%).

Abbreviations: SNP, single nucleotide polymorphism; CAP, community-acquired pneumonia; OR, odds ratio; CI, confidence interval.

Haplotype analysis of PTX3 SNPs

The linkage disequilibrium (LD) among the three SNPs of PTX3 was analyzed using Haploview software. Our results showed that a strong linkage disequilibrium was detected between rs2305619, rs3816527 and rs1840680 (Fig. 1), and four haplotypes were constructed for them, namely AAA, AAG, ACA and GAG (Table 4). We compared haplotype distributions between CAP group and control group, while no haplotype was identified to be associated with CAP ($p > 0.05$).

Table 4
Distribution of rs2305619,rs38716527 and rs1840680 common haplotypes in CAP patients and controls

Haplotype	CAP	Controls	*p*-value
AAA	9.9	14.4	0.18
AAG	5.7	4.6	0.62
ACA	18.5	21.0	0.54
GAG	63.4	57.1	0.23

Values are presented as Composition ratio. Those haplotypes whose distribution lower than 0.03 are ignored.

Abbreviations: CAP, community-acquired pneumonia

Discussion

In this study, we aimed to investigate whether the genetic variations of PTX3, including genotype, allele and haplotype frequency, is associated with CAP occurrence in Chinese adult patients. With respect to rs2305619, rs38716527 and rs1840680, we found that SNP rsl840680 AA homozygosity was associated with CAP occurrence. The AA variant of rsl840680 was related to a lower risk of developing CAP (OR = 0.32, 95% CI = 0.11–0.91, $p = 0.03$).

As a key player in innate immunity and inflammation, PTX3 plays an important role in the resistance to pathogens. Previous studies on the relationship between PTX3 and pulmonary bacterial infection have been mainly concentrated on *Pseudomonas aeruginosa* and *Streptococcus pneumoniae*. *P. aeruginosa* is one of the most common colonizers of the lung. PTX3 has potential therapeutic effects on chronic lung infections caused by *P.aeruginosa* [17]. According to a previous study in a mouse model infected with *P.aeruginosa*, PTX3 participated in the interaction between complements and Fcγ receptors, significantly decreasing serum levels of pro-inflammatory cytokines (CXCL1, CXCL2, CCL2 and IL-1β) and reducing leukocyte recruitment of airway leukocytes [18]. GroEL in *P. aeruginosa* could induce PTX3 expression via NF-κB activation following signaling to Toll-like receptor 4 (TLR4), and GroEL-induced PTX3 promoted macrophage binding and phagocytosis of bacteria [19]. To notice, *S. pneumoniae* is the most frequent etiologic agent of community-acquired pneumonia in adults. Research findings demonstrated that *S. pneumoniae* infection could up-regulate the expression of PTX3 in vitro and experimental models. Hemolysin secreted by *S. pneumoniae* was involved in PTX3 expression and up-regulation through the JNK-MAPK signaling pathway [20].

According to previous findings, PTX3 SNPs (rs2305619, rs3816527 and rsl840680) were associated with various infectious diseases. PTX3 polymorphism is closely related to the occurrence of tuberculosis in the West African population, and haplotype GAG is considered to be a protective factor [12]. Another study focused on Caucasian patients with cystic fibrosis which demonstrated that haplotype GAG was also a protective factor for the development of *P.aeruginosa* colonization in the lungs [13]. In addition, He.et al. reported that rs1840680 AA genotype might be a risk factor for developing fungal pulmonary infection in COPD patients [14]. Contrary to the findings of He.et al., we found that patients with the AA genotype of rsl840680 had a lower risk of developing CAP. Because bacteria were the most common causative pathogens in CAP, we assume that the same genotype might play a different role during infection with fungi and bacteria.

Our findings suggest that the rs1840680 AA genotype might be a protective factor against the development of CAP in adults. The mechanism of PTX3 gene driven by infections in the process may involve protein expression, but the relationship between PTX3 SNPs and protein levels still remains controversial. We assume that rs1840680 AA genotype may up-regulate the expression of PTX3 when patients suffer from pulmonary bacterial infection. Some studies have found that rs1840680 AA genotype was associated with increased protein level in patients with primary liver cancer and acute myocardial infarction [21–22]. In patients with idiopathic pulmonary dysfunction after lung transplantation, PTX3 protein expression level was also increased carrying rs2305619 AA genotype [23]. However, in COPD patients with invasive pulmonary aspergillosis, compared to AG and GG genotype, rs1840680 AA genotype decreased the protein expression level [14]. These paradoxical findings may lead to pitfall of interpretation, thus further investigation in different populations is needed to confirm the role of this SNP variation.

We are aware of several limitations in our current study. Firstly, our study population reflected mild to moderate patients but not including severe pneumonia. Secondly, our study was conducted at a single medical center. Therefore, the sample size was relatively small and selection bias may have occurred. Moreover, etiological investigations were mostly negative in CAP patients from this study, so according to clinical manifestations and laboratory tests, we could only choose patients with most likely bacterial infection while exclude definite fungal diseases and active tuberculosis. In the future, we hope to gather more extensive data from multiple institutions and carry out functional studies to determine the identified SNP on the risk of CAP.

Conclusions

In summary, our results support that PTX3 polymorphisms were associated with the risk of CAP in Chinese adult patients. Individuals with SNP rsl840680 AA homozygote may have a lower risk of developing CAP. Further research is required to clarify the specific mechanisms.

Abbreviations

CAP
community-acquired pneumonia
TNFR
tumor necrosis factor receptor
IL-1
interleukin-1
IRF-5
interferon regulatory factor-5
PTX3
pentraxin-3
CRP
c-reactive protein
SNP
single nucleotide polymorphism
COPD
chronic obstructive pulmonary disease
CTS
Chinese Thoracic Society

Declarations

Ethics approval and consent to participate:

This study has been approved by the Ethics Committee of Sun Yat-sen Memorial Hospital (number: SYSEC-KY-KS-2020-005).

Consent for publication:

Not applicable.

Availability of data and materials:

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests:

The authors declare that they have no competing interests.

Funding:

This work was supported by the National Natural Science Foundation of China [81670022]; the Guangzhou Municipal Science and Technology Project [201704020123]; and the Natural Science Foundation of Guangdong Province [2017A030313681].

Authors' contributions:

SPJ conceived and designed the study; TTT, LJH, QJZ, YQX, SYB, BRH, YMD, and ZXW had roles in clinical management and patient recruitment; YQX, SYB, YMD, BRH and ZXW contributed to data collections and data entry. YQX performed the statistics; TTT and YQX also performed the interpretation and manuscript writing. All authors reviewed and approved the final version of the manuscript.

Acknowledgements:

Not applicable.

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Figures

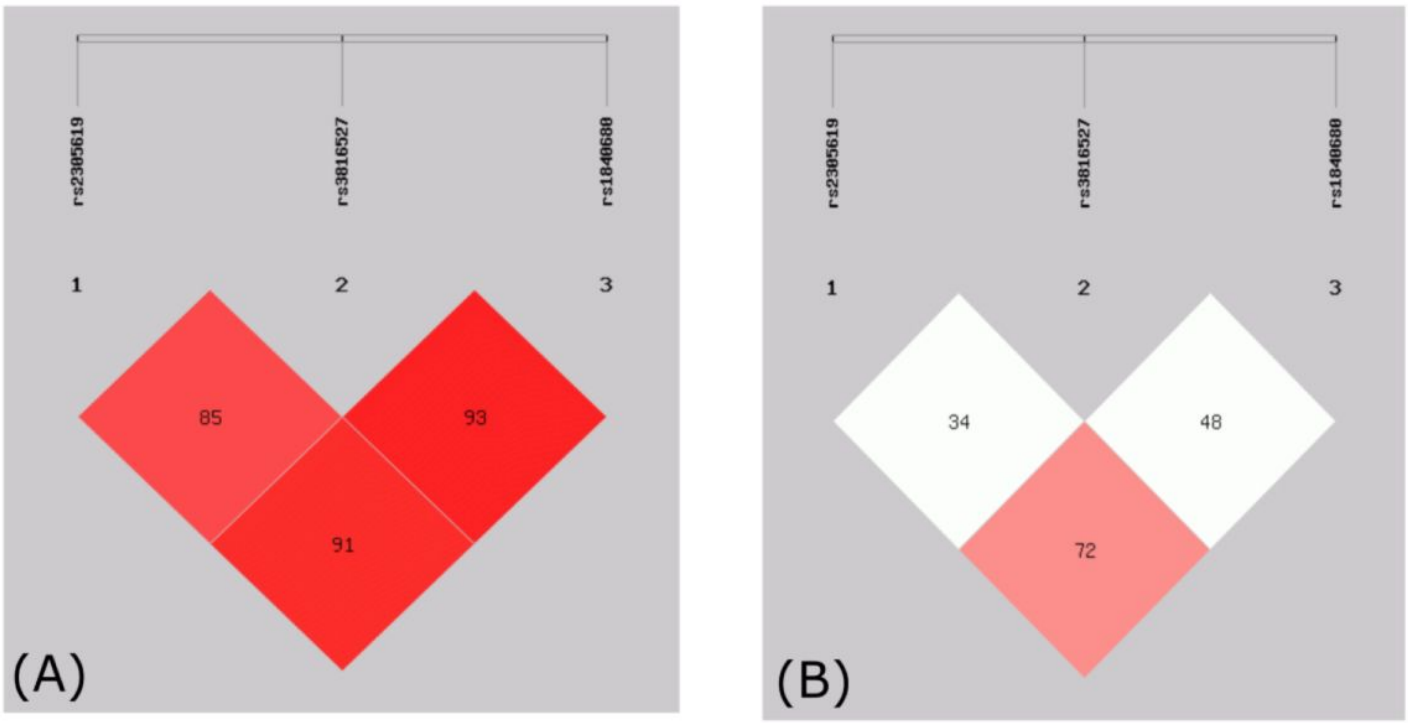

Figure 1

Linkage disequilibrium analyses for SNP genotype in the PTX3 gene region. (A) Shades of red indicated the strength of pairwise linkage disequilibrium based on |D'|, and numbers represent |D'| expressed as a percentage. A value of D' between SNPs > 0.8 indicate a linkage disequilibrium block. (B) Shades of pink indicated the strength of pairwise linkage disequilibrium based on r2 and numbers represent r2 expressed as a percentage.