



KCNA5 gene variation is not associated with the pulmonary hypertension in systemic sclerosis patients

Jiao Ai^{1,2#}, Mao Liu^{1,2#}, Zhuang Shuai^{1,2}, Kai Tang^{1,2}, Jiankang Zheng², Jinxi Yang², Lihan Peng²

¹Department of Clinical Medicine, North Sichuan Medical College, Nanchong 637000, China; ²Department of Cardiology, Cardiovascular Research Center, Affiliated Hospital of North Sichuan Medical College, Nanchong 637000, China

Contributions: (I) Conception and design: M Liu; (II) Administrative support: J Ai, M Liu; (III) Provision of study materials or patients: Z Shuai, K Tang; (IV) Collection and assembly of data: J Ai, J Zheng; (V) Data analysis and interpretation: M Liu, J Ai; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Mao Liu, MD, PhD. Department of Cardiology, Cardiovascular Research Center, Affiliated Hospital of North Sichuan Medical College, No. 63 Wenhua Rd. Nanchong 637000, China. Email: mliu.nsmc@outlook.com.

Background: The association between KCNA5 gene variation and systemic sclerosis-associated pulmonary hypertension (SSc-PAH) is unclear. The present meta-analysis was conducted to assess the association between KCNA5 gene variation and SSc-PAH.

Methods: Electronic databases were searched for relevant studies on the relationship between KCNA5 gene variation and SSc-PAH. Odds ratio (OR) with 95% confidence interval (CI) was selected as the effect scale indicators using a random-effects model. Statistical analysis was performed using RevMan 5.3 software.

Results: A total of 2 articles and 7,583 subjects were included. Among them, 298 were SSc-PAH patients. There was no significant difference found in the comparisons of C/C homozygotes (0.7% vs. 1.7%, OR=0.51, P=0.41), C/T heterozygotes (17.1% vs. 22.7%, OR=0.64, P=0.25) and C/C+C/T heterozygotes (17.8% vs. 24.4%, OR=0.59, P=0.25) between the two groups.

Conclusions: The pooled analysis of available data indicates that KCNA5 rs10744676 is not confirmed as an SSc-PAH genetic susceptibility factor.

Keywords: KCNA5; rs10744676; systemic sclerosis; pulmonary hypertension

Received: 25 June 2019; Accepted: 15 July 2019; Published: 06 August 2019.

doi: 10.21037/jxym.2019.07.04

View this article at: <http://dx.doi.org/10.21037/jxym.2019.07.04>

Introduction

Systemic sclerosis (SSc) is a multisystem autoimmune disease characterized by vasculopathy and tissue fibrosis of the skin and various internal organs (1). There is no cure for SSc, leading to significant morbidity, mortality and poor health-related quality of life (2). The prevalence varies greatly in recent reports, and most rates fall between 38 and 341 total cases/million (3).

SSc is a complex disease and its pathogenesis is not well understood. Pulmonary arterial hypertension (PAH) is a frequent and severe complication of SSc (4). Pathogenesis of PAH is complicated and multifactorial. The prevalence of PAH in SSc (SSc-PAH) has been estimated to be

between 5% and 12% (5). Some studies reported that the potassium voltage-gated channel shaker-related subfamily member 5 (KCNA5) rs10744676 might be linked to PAH, the results in different studies have been conflicting (6). Therefore, we performed a meta-analysis to assess the association of the KCNA5 rs10744676 polymorphism with the risk of SSc-PAH.

Methods

Search strategy

Firstly, the main literature databases at home and abroad (PubMed/Medline, EMBASE, Scopus, Cochrane Library,

CNKI, Wanfang database) were searched by computer, and then the references of related articles were searched twice to reduce missed detection. The following search terms were used: KCNA5, rs10744676, systemic sclerosis, pulmonary hypertension. The publication time of articles was set to the time of database construction until February 6, 2019. The language was limited to English and Chinese.

Inclusion and exclusion criteria

The original article types included in our study included cohort studies and case-control studies. Subjects must include SSc patients, SSc with PAH patients, and healthy controls. The original articles were to compare the KCNA5 gene variant (rs10744676) between SSc-PAH patients and healthy controls. If subgroup data is to be included, we select the group with more cases. Exclude animal studies, case reports, conference abstracts, reviews, drug trials, and languages other than Chinese or English, articles that do not have full text or incomplete data.

Data extraction and quality evaluation

Two researchers independently screened and read articles, and extracted article data. The quality evaluation was based on the Newcastle-Ottawa Quality Assessment Scale (NOS) of the case-control study. According to this scoring standard, a maximum of 9 points can be obtained for each case-control study. When the data extraction and quality evaluation process encountered inconsistencies, it was resolved through discussion.

Statistical analysis

The heterogeneity of each study was evaluated using the Cochrane Q test and I^2 . When $I^2 \geq 50\%$, there was heterogeneity between studies. In order to minimize bias, all meta-analytical steps in our study were selected as random effects models. The data of our study is the quantitative data, the odds ratio (OR) and 95% confidence interval (CI) are selected as the effect scale indicators. Funnel-plot was used to identify the publication bias. Except for the Cochrane Q test using $P < 0.1$ for the difference was statistically significant, the other tests were defined as $P < 0.05$ for the difference was statistically significant. Statistical analysis was performed using RevMan 5.3 software provided by the Cochrane Collaboration.

Results

Basic information of the articles included

By searching the Chinese and English databases, a total of 507 original articles were obtained. After eliminating the duplicates, reading the titles and abstracts, there were 3 articles satisfying the research topic. One of the 3 articles reported the gene mutation sites which did not match, as a result, it was excluded. Finally, 2 articles (7,8) were included in our research. Baseline data and search process are detailed in *Table 1* and *Figure 1*, respectively.

Relationship between KCNA5 gene mutation and SSc

As shown in *Figure 2*, a total of 7,583 subjects were included in the two articles, and the variation of KCNA5 gene in SSc patients and healthy controls was compared. The ratio of C/C homozygote was similar between the two groups (1.9% vs. 1.7%, OR=1.02, 95% CI: 0.57, 1.81, $P=0.95$), and the proportion of C/T heterozygotes in the SSc group was slightly higher (19.9% vs. 22.7%, OR=0.84, 95% CI: 0.73, 0.96, $P=0.008$), there was no significant difference in the proportion of C/C+C/T between the two groups (21.8% vs. 24.4%, OR=0.84, 95% CI: 0.70, 1.01, $P=0.06$).

Relationship between KCNA5 gene mutation and PAH

A total of 2 articles and 3,996 subjects were included, including 298 patients with SSc-PAH and 3,698 controls. There was no significant difference found in the comparisons of C/C homozygotes (0.7% vs. 1.7%, OR=0.51, 95% CI: 0.11, 2.48, $P=0.41$), C/T heterozygotes (17.1% vs. 22.7%, OR=0.64, 95% CI: 0.30, 1.37, $P=0.25$) and C/C+C/T heterozygotes (17.8% vs. 24.4%, OR=0.59, 95% CI: 0.24, 1.44, $P=0.25$) between the two groups (*Figure 3*).

Discussion

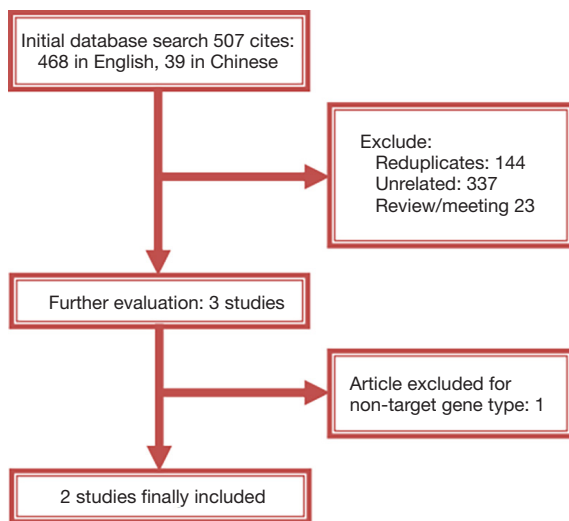
The present study performed a statistical analysis of the data from two original articles and found no significant differences in the ratio of KCNA5 gene mutations between patients with SSc-PAH and controls. The KCNA5 gene has not been confirmed to be an SSc-PAH genetic susceptibility factor.

SSc is a multisystem disease with vascular, inflammatory and fibrotic components, the mortality of SSc is high (9). PAH is a frequent complication of SSc and is one of the leading causes of morbidity and mortality in patients with

Table 1 Main characteristic of included studies

Items	Lara 2012	Wipff 2010
Research type	Case-control study	Case-control study
Region/race	Europe/Caucasians	Europe/Caucasians
Publication year	2012	2010
No. of participants	5,033	2,550
SSc	2,343	1,542
PAH	179	119
Control	2,690	1,008
Phenotype	rs10744676	rs10744676
KCNA5 test methods	TaqMan	TaqMan
Pulmonary artery pressure measurement	Right-heart catheterization	Right-heart catheterization
Criteria for PAH	Mean resting pulmonary artery pressure >25 mmHg and a pulmonary capillary wedge pressure ≤15 mmHg	Mean resting pulmonary artery pressure >25 mmHg and a pulmonary capillary wedge pressure ≤15 mmHg
NOS score	8	7

SSc, systemic sclerosis; PAH, pulmonary artery hypertension; NOS, Newcastle-Ottawa Scale.

**Figure 1** Screening process of the literature.

this disease, patients with SSc-PAH have a 3-year survival rate of 52% (10). The pathogenesis of PAH is complex and incompletely understood, but includes both genetic and environmental factors that alter vascular structure and function (11). Multiple genes have been shown to be associated with PAH, Nicholas *et al.* found that BMPR2, EIF2AK4, TBX4, ATP13A3, GDF2, SOX17,

AQP1, ACVRL1, SMAD9, ENG, KCNK3 and CAV1 genes have high evidence for causal effects in PAH (12). Single nucleotide polymorphisms in KCNA5 have been reported in PAH patients. It is suggested that KCNA5 is a genetic risk factor for the disease and KCNA5 has roles in determining pulmonary vascular tone, oxygen sensing, cell proliferation, and apoptosis (13,14). Although our data do not support an important role of KCNA5 rs10744676 as a PAH genetic marker in SSc patients. It is the first meta-analysis to analyze the association between KCNA5 and SSc-PAH, providing evidence-based medical evidence.

There are several potential limitations in this study. Firstly, only publications in English and Chinese were considered in the search process. Secondly, only two eligible studies and 7,583 participants were enrolled for meta-analysis, which was relatively few. Moreover, both of the studies were retrospective case-control studies which would lead to a recall bias inevitably. Therefore, all these contributed to the risk of bias in a certain degree. More large-scale studies are required in the future.

Conclusions

The pooled analysis of available data indicates that KCNA5 rs10744676 is not confirmed as an SSc-PAH genetic

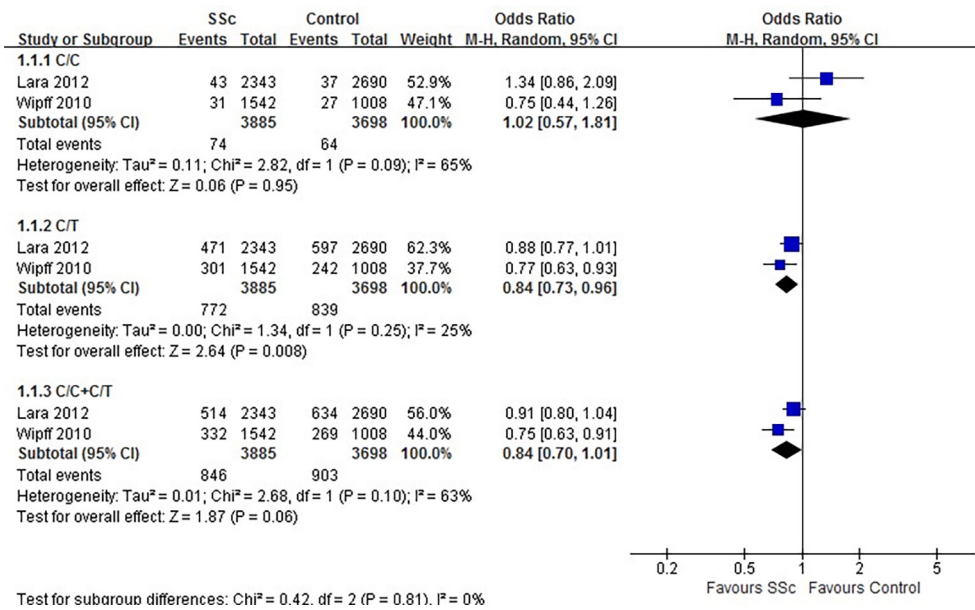


Figure 2 Forest plot of KCNA5 gene variation between SSc group and control group.

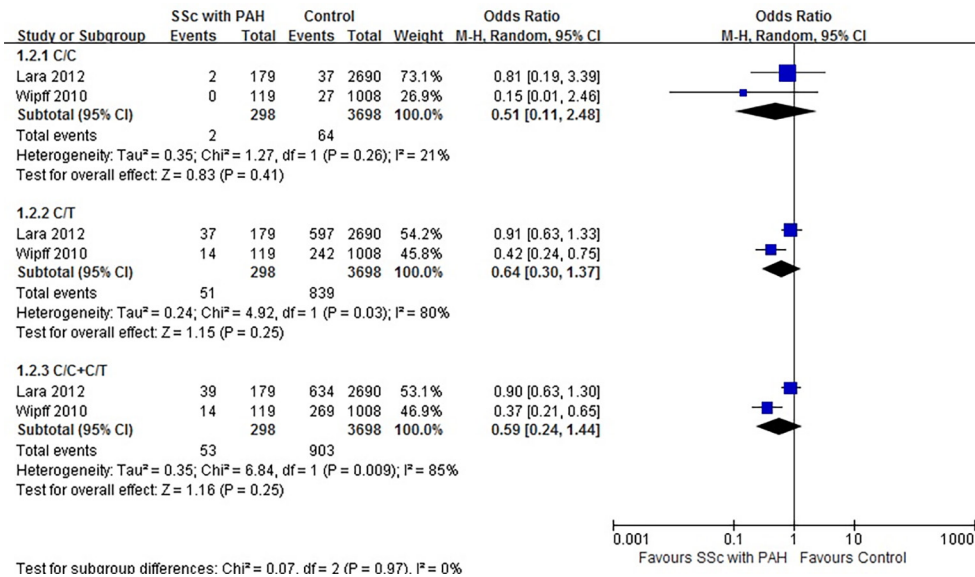


Figure 3 Forest plot of KCNA5 gene variation between PAH group and control group.

susceptibility factor.

Acknowledgments

Funding: The study was funded by Scientific Research Development Program of North Sichuan Medical College (CBY16-A-ZD10) and Nanchong Government-University

Strategic Cooperation Project in Science and Technology (18SXHZ0505).

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

- Asano Y. Systemic sclerosis. *J Dermatol* 2018;45:128-38.
- Morrisroe K, Stevens W, Sahhar J, et al. Epidemiology and disease characteristics of systemic sclerosis-related pulmonary arterial hypertension: results from a real-life screening programme. *Arthritis Res Ther* 2017;19:42.
- Ingegnoli F, Ughi N, Mihai C. Update on the epidemiology, risk factors, and disease outcomes of systemic sclerosis. *Best Pract Res Clin Rheumatol* 2018;32:223-40.
- Launay D, Sobanski V, Hachulla E, et al. Pulmonary hypertension in systemic sclerosis: different phenotypes. *Eur Respir Rev* 2017;26. doi: 10.1183/16000617.0056-2017.
- Sundaram SM, Chung L. An Update on Systemic Sclerosis-Associated Pulmonary Arterial Hypertension: a Review of the Current Literature. *Curr Rheumatol Rep* 2018;20:10.
- Jiao Y, Wang W, Lei P, et al. 5-HTT, BMPR2, EDN1, ENG, KCNA5 gene polymorphisms and susceptibility to pulmonary arterial hypertension: A meta-analysis. *Gene* 2019;680:34-42.
- Wipff J, Dieude P, Guedj M, et al. Association of a KCNA5 gene polymorphism with systemic sclerosis-associated pulmonary arterial hypertension in the European Caucasian population. *Arthritis Rheum* 2010;62:3093-100.
- Bossini-Castillo L, Simeon CP, Beretta L, et al. KCNA5 gene is not confirmed as a systemic sclerosis-related pulmonary arterial hypertension genetic susceptibility factor. *Arthritis Res Ther* 2012;14:R273.
- Tyndall AJ, Bannert B, Vonk M, et al. Causes and risk factors for death in systemic sclerosis: a study from the EULAR Scleroderma Trials and Research (EUSTAR) database. *Ann Rheum Dis* 2010;69:1809-15.
- Lefevre G, Dauchet L, Hachulla E, et al. Survival and prognostic factors in systemic sclerosis-associated pulmonary hypertension: a systematic review and meta-analysis. *Arthritis Rheum* 2013;65:2412-23.
- Ma L, Chung WK. The role of genetics in pulmonary arterial hypertension. *J Pathol* 2017;241:273-80.
- Morrell NW, Aldred MA, Chung WK, et al. Genetics and genomics of pulmonary arterial hypertension. *ur Respir J* 2019;53:S32-42.
- Remillard CV, Tigno DD, Platoshyn O, et al. Function of Kv1.5 channels and genetic variations of KCNA5 in patients with idiopathic pulmonary arterial hypertension. *Am J Physiol Cell Physiol* 2007;292:C1837-53.
- Moudgil R, Michelakis ED, Archer SL. The role of k⁺ channels in determining pulmonary vascular tone, oxygen sensing, cell proliferation, and apoptosis: implications in hypoxic pulmonary vasoconstriction and pulmonary arterial hypertension. *Microcirculation* 2006;13:615-32.

doi: 10.21037/jxym.2019.07.04

Cite this article as: Ai J, Liu M, Shuai Z, Tang K, Zheng J, Yang J, Peng L. KCNA5 gene variation is not associated with the pulmonary hypertension in systemic sclerosis patients. *J Xiangya Med* 2019;4:32.