Gene 509 (2012) 1–6

Contents lists available at SciVerse ScienceDirect

Gene

journal homepage: www.elsevier.com/locate/gene

Review

Association between the CTGF −945C/G polymorphism and systemic sclerosis: A meta-analysis

Xiufeng Zhang [a,b,c], Shengjie Nie [a], Xiaoyu Si [b,c], Ying Luo [b,c,*], Wenru Tang [b,c,*]

[a] School of Forensic Medicine, Kunming Medical University, Kunming, Yunnan 650500, China
[b] Faculty of Environmental Science and Engineering, Kunming University of Science and Technology, Chenggong Campus, 727 South Jingming Road, Kunming, Yunnan 650500, China
[c] Laboratory of Molecular Genetics of Aging & Tumor, Faculty of Life Science and Technology, Kunming University of Science and Technology, Chenggong Campus, 727 South Jingming Road, Kunming, Yunnan 650500, China

ARTICLE INFO

Article history:
Accepted 30 July 2012
Available online 11 August 2012

Keywords:
CTGF −945C/G
Meta-analysis
SSc

ABSTRACT

Background: The −945C/G polymorphism of the connective tissue growth factor (CTGF) has been associated with systemic sclerosis, however, results were conflicted. The aim of this study was to validate the evidence for the CTGF −945C/G polymorphism and systemic sclerosis risk.
Methods: Electronic search of PubMed was conducted to select studies. Case–control studies containing available genotype frequencies of −945C/G were chosen, and odds ratio (OR) with 95% confidence interval (CI) was used to assess the strength of this association.
Results: Six published case–control studies including 3335 cases and 3589 controls were identified. The overall results suggested that the variant genotypes were not associated with the systemic sclerosis risk (OR = 0.947, 95% CI: 0.792–1.132, p = 0.55). The stratified analysis in Caucasian (OR = 1.002, 95% CI: 0.837–1.2, p = 0.788) did not suggest an association either. However, analysis in Asian (OR = 0.632, 95% CI: 0.459–0.869, p = 0.005) showed that CC/CG genotype greatly decreased the susceptibility of systemic sclerosis in a dominant model. Asymmetric funnel plot, the Egger's test (p = 0.292), and the Begg's test (p = 0.593) were all suggestive of the lack of publication bias.
Conclusion: This meta-analysis supports that CC/CG genotype greatly decreased the susceptibility of systemic sclerosis in Asian. Due to the limited samples in subpopulations, further prospective studies with larger number of participants worldwide are needed to examine the association between the CTGF −945C/G polymorphism and systemic sclerosis.

Contents

Abbreviations: CTGF, connective tissue growth factor; SSc, systemic sclerosis; OR, odds ratio; CI, confidence interval; TGF, transforming growth factor; SNP, single nucleotide polymorphism; HWE, Hardy Weinberg-Equilibrium.

* Corresponding authors at: Laboratory of Molecular Genetics of Aging and Tumor, Faculty of Life Science and Technology, Kunming University of Science and Technology, Kunming University of Science and Technology, Chenggong Campus, 727 South Jingming Road, Kunming, Yunnan 650500, China. Tel.: +86 871 5920753; fax: +86 871 5920753.
E-mail addresses: xiuzheng1203@163.com (X. Zhang), luoyingabc@yahoo.com (Y. Luo), twr@sina.com (W. Tang).

0378-1119/$ – see front matter © 2012 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.gene.2012.07.061

1. Introduction

Systemic sclerosis (SSc), characterized by extensive organ fibrosis, vascular abnormalities and immune system dysfunction, is an autoimmune disorder. One of the main hallmarks of this disease is the microvascular involvement, which leads to the impairment of the blood flow to the hands, arms, face and vital organs. SSc affects several organs or tissues, including the skin, lung, heart and kidney, that results in significant mortality and morbidity (Agarwal et al., 2008; Denton et al., 2006; Reveille, 2005). By its progression, SSc can be divided into two groups: limited and diffuse SSc. At present, the molecular mechanisms and pathogenesis of SSc have not been clearly understood. Over the past years, it has been indicated that environmental factors as well as genetic risk factors are shown to be involved in this disease (Adiga et al., 2008; Agarwal, 2010; Ranque and Mouthon, 2010). To date the reports about the role of environmental factors in the progression of SSc are still ambiguous. The genetic studies have shown that multiple genetic risk factors or specific gene–gene interactions are found in patients with SSc (Broen et al., 2012; Fox and Kang, 1992; Gourh et al., 2009; Mayes and Trojanowska, 2007). Recently, a number of studies suggest that connective tissue growth factor (CTGF) gene polymorphism plays an important role in the progression of SSc (Fonseca et al., 2007; Kawaguchi et al., 2009). Thus, the CTGF could be used as a genetic marker and shed light in explaining the pathogenesis of SSc.

Connective tissue growth factor (CTGF) is a member of CCN family of secreted proteins. CTGF is a chemotactic and adhesive factor responsible for growth. It is transcriptionally activated by transforming growth factor (TGF) (Abreu et al., 2002; Tall et al., 2010). CTGF is frequently found overexpressed in many human disorders, especially on the tissue fibrosis (Shi-Wen et al., 2008). It has been shown that CTGF could carry out its biological activity by activating Akt, MAPK or ERK1/2 signal pathways. It could also bind to and activate the cell surface integrin and promote cancer invasion (Chen et al., 2007; Perbal, 2004). Patients with SSc frequently showed increased CTGF expression in the skin and fibroblasts. This suggests that the CTGF gene could act as a new genetic marker for SSc susceptibility (Frazier et al., 1996; Igarashi et al., 1995, 1996). To date, a number of studies indicate that a single nucleotide polymorphism (SNP) −945C/G in the CTGF promoter is associated with the susceptibility of SSc (Fonseca et al., 2007; Kawaguchi et al., 2009). However, some studies suggest that the −945C/G polymorphism in the CTGF promoter has no association with the SSc susceptibility (Gourh et al., 2008; Granel et al., 2010; Louthrenoo et al., 2011; Rueda et al., 2009). Therefore, we conducted a meta-analysis to assess the effect of the −945C/G polymorphism in the CTGF gene on the risk of SSc.

2. Materials and methods

2.1. Publication search

PubMed was searched using the search terms 'CTGF or CCN2', 'polymorphism' and 'systemic sclerosis' or 'SSc' (the last search update was on Jan 18, 2012). Case–control studies containing available genotype frequencies of −945C/G were chosen. Additional studies were identified by a manual search of the references of original studies. Of the studies with overlapping data published by the same investigators, only the most recent or complete study was included in this meta-analysis.

2.2. Inclusion and exclusion criteria

Inclusion criteria: (1) to validate the association between the CTGF −945C/G promoter polymorphism and systemic sclerosis; (2) usage of a case–control, cohort design; (3) enough data were calculated to estimate the odds ratio (OR) and 95% confidence interval (CI). Major exclusion criteria as: (1) no control subjects; (2) there were insufficient data to estimate the relative risk (OR); (3) no usable genotype distribution or allele frequency data.

2.3. Statistical analysis

For control group of each study, the observed genotype frequencies of the −945C/G polymorphism in the CTGF gene were assessed for Hardy Weinberg-Equilibrium (HWE) using the χ^2 test. The strength of

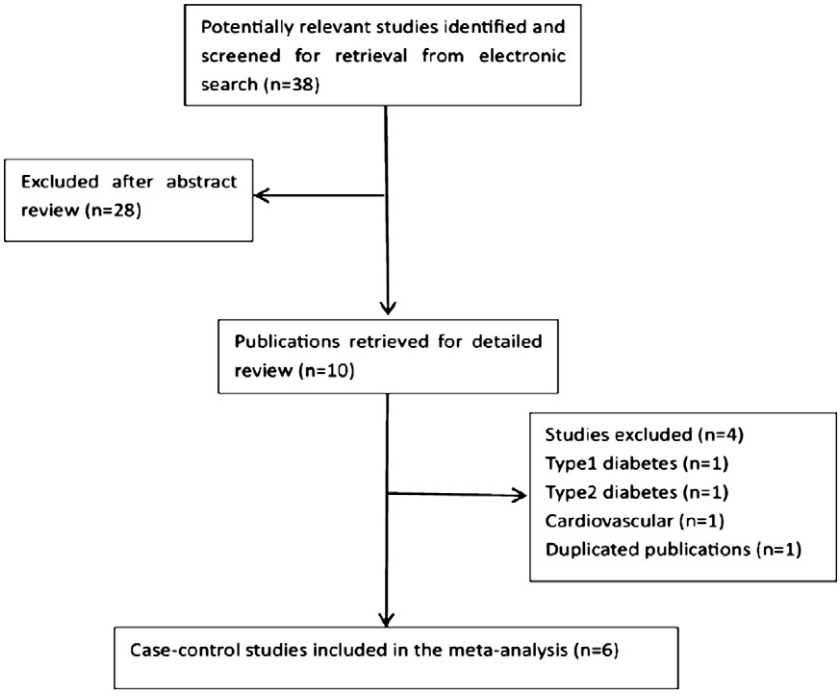

Fig. 1. Flowchart of the study selection procedure.