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# Influence of component 5a receptor 1 (*C5AR1*) −1330T/G polymorphism on nonsedating H1-antihistamines therapy in Chinese patients with chronic spontaneous urticaria

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ABSTRACT

*Background:* The nonsedating H1-antihistamines are the first-line medicines for chronic spontaneous urticaria (CSU) patients. However, not all these patients respond well to the antihistamines, and the mechanisms underlying the interindividual differences are still unclear. *C5AR1* gene encodes the component 5a receptor (C5aR) protein, which has been reported to play an important role in chronic spontaneous urticaria.
*Objective:* This study aimed to investigate whether the single nucleotide polymorphisms (SNPs) in *C5AR1* are associated with CSU susceptibility and antihistamines therapeutic efficacy in Chinese CSU patients.
*Methods:* A total of 191 CSU patients and 102 healthy controls were prospectively studied in our study. CSU patients were treated by nonsedating H1-antihistamines monotherapy for 4 weeks. The *C5AR1* −1330T/G (rs11673309) genotype was determined by Sequenom Massarray.
*Results:* Among these 191 CSU patients, there were 114 patients who were treated with desloratadine, 65 were treated with mizolastine, and 12 with fexofenadine. The−1330T alleles in CSU patients were significantly higher than controls (0.555 vs. 0.466, $P = 0.040$, OR = 1.429 [1.016–2.010]). The poorest response to desloratadine was observed in heterozygotes, when compared with either GG or TT homozgote ($P = 0.001$). However, there was no significant difference in three genotypes when treated with mizolastine group ($P = 0.215$).
*Conclusion:* We concluded that the *C5AR1* SNP −1330T/G may serve as a useful pharmacodynamic predictor of nonsedating H1-antihistamines efficacy in CSU patients, and −1330T alleles may be taken as a risk factor for the CSU.


## 1. Introduction

Urticaria is a common disease characterized by histamine release through mast cell activation accompanied by inflammatory responses. The prevalence of the disease varies from 15% to 30% worldwide [1]. Eventually about 20% of the cases develope into chronic spontaneous urticaria (CSU) [2], whose clinical features are defined as spontaneous wheals daily, or almost daily, lasting for more than 6 weeks without an identifiable cause [3]. And the affected individuals show a significantly impaired quality of life (QoL) [4,5].

Complement component 5a (C5a) is one of the most potent inflammatory peptides with abundant biological functions, such as degranulation, granule enzyme release, apoptosis, chemokine and cytokine production [6]. Through modulating the complement C5a pathway, C5a receptor (C5aR) plays an important role in the mast cell activation and degranulation, and thus augments histamine release [7]. Therefore, we suppose that the expression of C5aR on the surface of the response cells, for instance, mast cells and basophils, may play a role in the etiology of CSU. Human C5aR is

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encoded by *C5AR1* (also known as *C5AR*) gene, and previous studies have reported that there are some associations between *C5AR1* gene or genetic polymorphisms and some kinds of immune diseases, such as familial Mediterranean fever and arthritis [8–10]. Several single nucleotide polymorphisms (SNPs) in the *C5AR1* gene locus have been discovered, which include the promoter SNPs at position −245 (T/C) [8], SNPs in the coding region 4G/A, 859G/T, 72T/C, 727G/A, 450C/T and 279N/K [9,11]. However, the association between SNPs of *C5AR1* and CSU susceptibility has not been reported. The SNP rs11673309 (−1330T/G) has already been discovered in some populations (http://asia.ensembl.org/Homo_sapiens/Variation/Population?db=core;r=19:47811323-47812323;v=rs11673309;vdb=variation;vf=7947374). However, there is no study regarding the association of this SNP with any disease. In this study, we wonder whether *C5AR1* polymorphisms would manifest as different phenotypes in CSU.

Antihistamines are a group of drugs commonly used in the treatment for CSU. The symptoms of CSU can relieve significantly with nonsedating H1-antihistamines therapy, but the clinical outcome varies. In a study of 390 CSU patients treated with H1-antihistamines, apart from 23% patients who missed follow-up, 44% patients responded well, 15% showed partial relief, while at least 17% patients showed little or no benefit [12].

Desloratadine, mizolastine and fexofenadine are three widely used antihistamines in the treatment for urticaria in clinical practice [13–15]. A study has shown that 42.7% cases have a complete relief of signs and symptoms of CSU, and 45.6% have a significant relief of symptoms, whereas 11.7% have a moderate relief by desloratadine therapy [16]. Similar to desloratadine, mizolastine has diverse response among CSU patients [17], and the inefficacy rate is about 28% after mizolastine therapy [18]. For fexofenadine, it has been reported that 53.3% patients shows no improvement while others achieve whole or partial improvement after treatment by fexofenadine [19]. However, the mechanisms of the efficacy underlying the interindividual variability with H1-antihistamines are unknown.

Pharmacogenetics is widely used to explore the effects of genetic factors on drug disposition and efficacy [20]. Evidence has shown that genetic polymorphisms of genes coding the drug metabolism enzymes, drug targets and diseases mechanism may partially account for the inter individual variation in therapeutic efficacy of drug. In view of the fact that C5a/C5aR pathway plays a crucial role in augmenting histamine release and leads to the inflammatory response of CSU, we evaluate the impacts of *C5AR1* polymorphisms on CSU susceptibility and H1-antihistamines efficacy in Chinese patients in this study.

## 2. Materials and methods

### 2.1. Patients

This prospective study was conducted at the Department of Dermatology, XiangYa Hospital, Central South University from August 2012 to October 2013. The study was approved by the Ethics Committees of XiangYa Hospital. The registration number of Chinese Clinical Trial Registry online is ChiCTR-OCH-14004518, and the protocol is available at URL:http://www.chictr.org/cn/proj/show.aspx?proj=8045. Chronic spontaneous urticaria patients enrolled in this study were from Southern Han Chinese population. The inclusion criteria were: (i) patients fulfilled the diagnostic criteria for CSU [3]; (ii) patients aged ≥18 years; (iii) no antihistamines, antidepressants, corticosteroids, leukotriene and any other medicines were received in the prior two weeks before enrollment. (iv) No sensitive, allergy or previous adverse reaction to antihistamines. The exclude criteria for the patients were as follows: (i) had other dermatological conditions or any other disease (e.g. autoimmune diseases, thyroid diseases, infectious diseases, psychosomatic and psychiatric diseases), required pharmacologic treatment or use of drugs (NSAIDs, injections, immunizations, hormones, etc.); (ii) hereditary angioedema, urticarial vasculitis, and chronic inducible urticaria; (iii) pregnant women or breastfeeding mothers [21,22]. Totally, 191 CSU patient and 102 healthy controls were studied. Written informed consent was obtained from each patient before participating in this study. Demographic as well as clinical data of the CSU patients were collected. Demographic data included gender, age, height, weight, and BMI. Clinical presentations including the weekly urticaria activity score(UAS7) [23], duration of the disease, accompanying symptoms, personal and family history of atopic disease, treatments, side-effects, and routine laboratory test results including complete blood cell count, biochemistry, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) were recorded.

### 2.2. Measurements

Chronic spontaneous urticaria disease activity was assessed by the UAS7 as suggested in the guideline [3]. The Dermatology Life Quality Index (DLQI) was a simple and reliable parameter to assess the quality of life for the patients suffered from dermatological disease [21]. Patients were treated by monotherapy for 4 weeks, desloratadine 5 mg/d, mizolastine 10 mg/d, or fexofenadine 120 mg/d, respectively. All patients were required to complete the DLQI questionnaire and UAS7 diary before and after therapy. Diagnosis and clinical efficacy of antihistamines were assessed by two professional dermatologists. The efficacy of the treatment was assessed with the UAS7 scores according to the guideline suggested [3]. Response was defined as the UAS7 scores achieving a 50% or greater improvement compared with the baseline UAS7, while an improvement below 50% was regarded as non-response [3,23–25].

### 2.3. SNPs selection and genotyping

Five milliliters venous blood from each participant was drawn for genotyping. All the blood samples were stored at −80 °C until used. Genomic DNA was extracted from whole blood with a FlexiGene DNA Kit in accordance with the protocols of the manufacturer (Qiagen, Hilden, Germany). According to the reported database of Southern Han Chinese (CHS) population in the 1000 genomes Project http://browser.1000genomes.org/Homo_sapiens/Variation/HighLD?db=core;r=19:47811323-47812323;v=rs11673309;vdb=variation;vf=7974300#102183_tablePanel, a SNP rs11673309 T>G (−1330T/G) in the *C5AR1* promoter was selected and genotyped in our study. The SNP was in linkage disequilibrium with variations including rs73063338, rs4595896, rs4427917, rs11670330, rs10404456, and others. This polymorphism was genotyped by the method of allele-specific matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (Sequenom, Inc., CA, USA) [26]. All the samples using Sequenom were examined carefully and only when the positive rate of a genotype matching the SNPs more than 99.5% was certified. At the same time, 102 age- and gender-matched healthy controls were also genotyped by direct sequencing for SNP *C5AR1* −1330T/G.

### 2.4. Statistical analysis

All the analyses were performed in the SPSS 13.0 statistical package (IBM SPSS, Chicago, Illinois). Allele frequency distributions in different subgroups and Hardy–Weinberg equilibrium were tested by chi square analysis method. The UAS7 and DLQI before and after-treatment were analyzed by paired-samples *t*-test. Differences in a series of variables such as CRP, ESR, score change