PSORS1C1 gene polymorphism is associated with autoimmune thyroid diseases in the Chinese population

CURRENT STATUS: UNDER REVIEW

BMC Medical Genetics  ■ BMC Series

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DOI:
10.21203/rs.2.24297/v1

SUBJECT AREAS
Medical Genetics

KEYWORDS
Graves' disease(GD), Hashimoto's thyroiditis(HT), the psoriasis susceptibility 1 candidate 1(PSORS1C1), single nucleotide polymorphism(SNP)
Abstract

Objective Autoimmune thyroid disease (AITD) is not only an immune-related disorder, but also inherited as a complex gene-related disease. The psoriasis susceptibility 1 candidate 1 (PSORS1C1) gene is a susceptibility locus in autoimmune diseases. Many autoimmune diseases have been proved to be related with the PSORS1C1 gene. However, whether the PSORS1C1 gene plays a role in affecting the predisposition to AITD remains unknown.

Methods In this study, we included 1056 Chinese Han AITD patients and 954 matched healthy controls. Multiplex polymerase chain reaction (PCR) technology was used to genotype SNPs (rs3130983, rs3778638, rs3815087, rs4959053)in PSORS1C1 gene.

Results An association between rs3778683 and Graves' disease (GD) was observed with statistical significance (p=0.039). The allele and genotype of single nucleotide polymorphism (SNP) rs3130983, rs3815087 and rs4959053 showed no significant association with AITDs. In addition, no linkage disequilibrium for rs3130983, rs3815087, rs3778638 and rs4959053 in PSORS1C1 gene was found between AITD patients and controls.

Conclusion These data revealed the influence of PSORS1C1 on the susceptibility to AITDs and reinforced this locus as a common autoimmunity risk factor.

Introduction

Autoimmune thyroid diseases (AITDs) mainly include Graves' disease (GD) and Hashimoto's thyroiditis (HT). Recent epidemiological studies showed that the incidence of AITD has risen steadily, affecting about 5% of the general population [1, 2]. It is one of the most prevalent autoimmune diseases. In the pathological process of AITD, both cellular and humoral immune responses against the thyroid gland are involved, but the exact mechanism is not clear now [3].

The etiology of AITD is mainly due to the complex interplay of specific susceptibility genes and environmental exposures. Through family and population studies, the strong genetic influence and inheritability in the development of AITD have been confirmed. Linkage and association analyses, genome screening, and genome wide association studies (GWAS) [4] in genes have been discovered to be associated with AITD. These genes include thyroid-self antigen genes such as the TSH receptor.
(TSHR) [5] and thyroglobulin (TG) gene [6]), and immune-modulating genes such as FOXP3 [7], CD25 [8], CD40 [9], CTLA-4 [10] and HLA [11]. We have confirmed several genes through several single nucleotide polymorphisms (SNPs), in particular like TG [6], interleukin-17 [12] polymorphisms. All the above are significantly contribute to the predisposition for GD and HT.

The psoriasis susceptibility 1 candidate 1 (PSORS1C1) is located 127 kb distal to the HLA-C locus on chromosome 6p21.3 [13], near to the structure of antigen presentation (T cell activation) on HLA locus on chromosome 6p21. PSORS1C1 gene predominantly confers susceptibility to psoriasis, an immune-mediated skin disease [14, 18]. Recently, several studies showed the association of PSORS1C1 with other systemic autoimmune disorders or immune-related diseases such as rheumatoid arthritis (RA) [13], ankylosing spondylitis [15], systemic lupus erythematosus (SLE) [16], multiple asthma [17], the Systemic Capillary Leak Syndrome [19], and systemic sclerosis (SS) [20]. Thence, we hypothesize that PSORS1C1 gene is a common susceptibility gene for variant of autoimmune diseases. However, until now, little is known about the association between PSORS1C1 and AITD.

In this study, we firstly carried out a large case-control study in a cohort of the Chinese Han population to investigate the genetic association between PSORS1C1 gene and AITD. We selected 4 SNPs (rs3130983, rs3778638, rs3815087, rs4959053), furthermore, analyzed the association between genotypes and AITD clinical phenotypes.

Materials And Methods
This was a case-control study performed at the outpatient department of Endocrinology Department in the Jinshan Hospital of Fudan University during 2012.1-2014.12. The research project was approved by the ethics committee of the hospital. While individuals younger than the age of 18, who consent to participate had been obtained from their parents or legal guardians. The obtained from the parents of the patient was written in the medical record book.

Subjects
This case control study investigated a total of 2019 non-related Chinese Han subjects, including 1065 patients with AITD (702 GD patients, 363 HT patients) and 954 healthy controls (326 males and 633 female; aged 20-75 years). These GD patients were aged between 5 and 77, including 487 women.
and 203 men. Meanwhile, HT patients were aged between 4 and 78, including 316 women, 45 men. While, family history of any autoimmune thyroid diseases, thyroid size and ophthalmopathy were selected and detailed information of the subjects was shown in Table 1. All the AITD patients were treated in the outpatient department of Endocrinology Department in the Jinshan Hospital of Fudan University. There is a rigorous screen for these patients, it is used to choose patients without suffering from other autoimmune diseases, and without other chronic visceral diseases or overt diseases. The healthy controls come from the health examination center of the same hospital. The diagnostic criteria of GD were according to clinical manifestations, laboratory biochemical hyperthyroidism test results, the presence of diffuse goiter, and the presence of thyrotropin receptor antibodies. HT requires associated with the presence of TPOAb or TGAb, with or without documented clinical and biochemical hypothyroidism. Few difficult diagnosed HT patients are further confirmed by fine needle aspiration biopsy (FNAC) technology. All the subjects gave the informed consent.

Table 1
Clinical data of AITD patients and controls

|                  | GD(%)  | HT(%)  | Control(%) |
|------------------|--------|--------|------------|
| **Number**       | 703(35)| 362(18)| 943(47)    |
| **Gender**       |        |        |            |
| Female           | 488(69.4) | 317(87.6) | 632(67) |
| Male             | 215(33.6) | 45(12.4)  | 311(33)   |
| **Age**          |        |        |            |
| 36.9 ± 14.59     | 34.82 ± 0 | 38.56 ± 9.423 |
| **Onset of age** |        |        |            |
| 36.44 ± 14.75    | 37.77 ± 12.72 |
| **Thyroid size** |        |        |            |
| Normal           | 87(13)  | 49(14.2) |            |
| I                | 117(17.5)| 50(14.5) |            |
| II               | 371(55.5)| 218(63.4)|            |
| III              | 93(13.9)| 27(7.8)  |            |
| **Family history** |   |        |            |
| (+)              | 535(80)| 71(20.8) |            |
| (-)              | 133(20)| 270(79.2)|            |
| **Ophthalmopathy** | |        |            |
| (+)              | 127(20.1)| 7(2)     |            |
| (-)              | 504(79.9)| 335(98)  |            |

Clinical phenotype analysis

Our research investigated 1065 AITD patients including 703 GD (33.6% male and 69.4% female) and 362 HT (12.4% male and 87.6% female). In GD patients, the average age of onset was 36.9 ± 14.59, 535(80%) individuals had family history and 121 (20.7%) had ophthalmopathy. In HT patients, the average age of onset was 34.82 ± 0, 71 (20.8%) individuals had family history and 7 (2%) had ophthalmopathy. In addition, it is not entirely uniform distribution of thyroid size's degree in GD and HT group, the degrees (normal size, the degrees I, II, III) of thyroid size in GD group were
13%, 17.5%, 55.5%, and 13.9%, respectively, and in HT were 14.2%, 14.5%, 63.4%, 7.8%, respectively.

**SNP genotyping**

In our research, we collected peripheral venous blood of 2 ml from every subject. The Relax Gene Blood DNA System (Tiangen Biotech Co., Ltd., Beijing, China) was used to extract DNA from the peripheral blood cells according to the manufactures' guidelines. SNPs (rs3130983, rs3778638, rs3815087, rs4959053) was performed by Shanghai Biowing Applied Biotechnology Company(http://www.biowing.com.cn). The concentration and purity of each DNA sample were operated by Nano Drop 2000 Spectro-photometer (Thermo Scientific Compan, Waltham, Ma, USA). We designed primers from the Hapmap CHB data(http://hapmap.ncbi.nlm.nih.gov/) using Haploview Software 4.2. Polymerase chain reaction (PCR) technology for DNA amplification of the target gene.

The target genes and primer sequences are shown as follows:

| SNP       | UPPER             | LOWER             | SIZE |
|-----------|-------------------|-------------------|------|
| RS3130983 | CAAGTAGGGAATGGCTCTG | GGGATGTCCGAACTACA | 167  |
| RS3778638 | TGTGAAACAGGGGGAAAG | TCCATAAAGAGGAGGCTTG | 151  |
| RS3815087 | GACTCTGCAGCCACCATC | ACCAAGTGCCTGCCACAG | 150  |
| RS4959053 | TTTCTGGGGAATCCAATC | TGCATGGGTCACTGTACC | 197  |

**Statistical Analysis**

In this study, we adopted a case-control method and processed all the data in the distributions of characteristics variables by Chi-square test (SPSS version 17.0 Software). Between cases and controls, the haplotype frequencies of SNPs Differences, allele and genotype frequencies of four SNPs between the patients and controls were estimated also by the Chi-square test. A P value of < 0.05 was considered significant. On the other hand, the odds ratio (OR) and 95% confidence intervals (95% CI) were used cooperatively to assess the correlation between genotype and AITD. Linkage disequilibrium (LD) between SNPs was evaluated by pair of LD measure D ' and r^2 though the Haplotype frequency calculated by means of Haploview4.2 (Broad Institute) which on NCBI (version 4.2; http://www.broadinstitute.org/haploview/haploview).

**Results**

The results of genotype and allele distributions of the PSORS1C1 gene polymorphism for each
subgroup are summarized in Table 3. It showed that the genotype distribution of these four SNPs was different at rs3778638 genotype in AITD group (AA, 2.67%; AG, 19.15% and GG, 78.18%) and normal control group (AA, 1.52%; AG, 22.2% and GG, 75.87%) \( (P = 0.046) \) (Table 4). When Graves’ disease (GD) or Hashimoto’s thyroiditis (HT) patients were analyzed separately, the differences in genotype frequencies were significantly associated with GD \( (P = 0.039) \), not HT \( (P = 0.141) \) (Table 5). But for the remainders of rs3130983, rs3815087 and rs4959053, there wasn’t any significant difference in AITD patients group and the control group, both in genotypes and alleles.

**Table 3**

Allele distribution of the PSORS1C1 gene in AITD patients and controls

| SNP    | Allele | AITD(%) | Control(%) | P      | OR    | 95% CI       |
|--------|--------|---------|------------|--------|-------|--------------|
| rs3130983 | C      | 506(50) | 506(50)    | 0.064 | 0.874 | 0.757–1.008  |
|         | T      | 1534(53.38) | 1340(46.62) | 0.583 | 0.948 | 0.784–1.147  |
| rs3778638 | A      | 248(51.13) | 237(48.87) | 0.583 | 0.948 | 0.784–1.147  |
|         | G      | 1778(52.46) | 1611(47.54) | 0.542 | 0.960 | 0.841–1.096  |
| rs3815087 | T      | 692(51.60) | 649(48.40) | 0.542 | 0.960 | 0.841–1.096  |
|         | C      | 1330(52.67) | 1197(47.33) | 0.542 | 0.960 | 0.841–1.096  |
| rs4959053 | A      | 195(50.65) | 190(49.35) | 0.541 | 0.936 | 0.758–1.156  |
|         | G      | 1791(52.29) | 1634(47.71) | 0.541 | 0.936 | 0.758–1.156  |

**Table 4**

Genotype distribution of the PSORS1C1 gene in AITD patients and controls

| SNP    | Genotypes | AITD(%) | Control(%) | \( \chi^2 \) | P      |
|--------|------------|---------|------------|----------------|--------|
| rs3130983 | CC        | 67(6.57) | 68(7.51)   | 3.825          | 0.148  |
|         | CT        | 372(36.47)| 365(40.29) |                |        |
|         | TT        | 581(56.96)| 473(55.21) |                |        |
| rs3778638 | AA        | 27(2.67) | 14(1.54)   | 6.150          | 0.046  |
|         | AG        | 194(19.15)| 209(23.04) |                |        |
|         | GG        | 792(78.18)| 684(75.50) |                |        |
| rs3815087 | CC        | 448(44.31)| 388(42.87) | 0.365          | 0.833  |
|         | CT        | 434(42.93)| 395(43.65) |                |        |
|         | TT        | 129(12.76)| 122(13.48) |                |        |
| rs4959053 | AA        | 8(0.81)  | 12(1.34)   | 1.214          | 0.545  |
|         | AG        | 179(18.26)| 164(18.34) |                |        |
|         | GG        | 806(80.93)| 718(80.31) |                |        |

**Table 5**

The rs3778638 genotype distribution in patients with GD and HT and controls

| Genotypes (rs3778638) | GD(%) | Control (%) | GD vs. Controls \( (\chi^2 / P) \) | HT(%) | Control (%) | HT vs Controls \( (\chi^2 / P) \) |
|------------------------|-------|-------------|-----------------------------------|-------|-------------|----------------------------------|
| AA                     | 16(53.33) | 14(46.67) | 6.480/0.039                     | 11(44) | 14(56) | 3.913/0.141                      |
| AG                     | 122(36.86) | 209(63.14) | 209(74.38)                      | 209(74.38) | 701(72.49) |                                  |
| GG                     | 544(43.69) | 701(56.31) | 701(72.49)                      | 701(72.49) | 701(72.49) |                                  |

By using the Haploview 4.2 (Daly Lab at the Broad Institute, Cambridge, MA02141, USA), we found there was no linkage disequilibrium for gene’s rs3130983, rs3815087, rs3778638 and rs4959053 between AITD patients and controls in the distribution of the haplotypes (Fig. 1). And in the presence of linkage disequilibrium (LD) in block (Table 4), there are only two loci (rs3815087, rs4959053) in the
same LD block. The reference $r^2$ value is 0.059. This illustrated that the group does not exist
genetic locus linkage disequilibrium nature. From Table 6 and Table 7, we can see the group gene
allele and haplotype frequencies were not statistically different, too.

Table 6
Haplotype association analysis of rs3130983, rs3778638, rs3815087, rs4959053

| Haplotype Associations | Frequency | $\chi^2$ | P     |
|------------------------|-----------|----------|-------|
| CG                     | 55.2%     | 0.987    | 0.321 |
| TG                     | 34.7%     | 0.359    | 0.549 |
| CA                     | 10.1%     | 0.481    | 0.488 |

Table 7
Allele association analysis of rs3130983, rs3778638, rs3815087, rs4959053

| SNP        | Allele Associations | $\chi^2$ | P     |
|------------|---------------------|----------|-------|
| rs3130983  | C                   | 3.231    | 0.0723|
| rs3778638  | T                   | 0.362    | 0.5474|
| rs3815087  | A                   | 0.388    | 0.5332|
| rs4959053  | A                   | 0.316    | 0.5739|

Even grouped with gender, disease onset of age, thyroid size, family history, different course of
diseases and GO, all the four SNPs were analyzed by genotype and allele distribution. Unfortunately,
no significant difference was observed ($p > 0.05$) to those clinical phenotypes.

Discussion
In various immune-mediated inflammatory diseases, the presence of shared genetic basis can be
found. The HLA region is the most common region, which has strong disequilibrium to autoimmune
disease. PSORS1C1, a 250 kb region encompassing major histocompatibility complex (MHC) [13, 21, 22]. In numerous studies of in varied populations, this gene has consistently been implicated in the
susceptibility to psoriasis[23–25].

In genomic DNA, different sequence alternatives (alleles) exist in normal individuals. The potential
changes of amino acid sequence of a gene could cause changes in gene function [32]. These changes
could influence the susceptibility of diseases directly. Therefore, the variety inside a gene of SNPs
allele could make contribution to a specific disease, and affect the susceptibility to the disease.

Investigating the genetic polymorphism of PSORS1C1 with autoimmune diseases, rs3130983,
rs3778638 and rs4959053 in the PSORS1C1/CDSN locus have been reporting a significant association
of the PSORS1C1 gene single nucleotide polymorphism (SNP) with RA[13]. Some single nucleotide
polymorphisms(SNPs) in PSORS1C1 have been shown to predict susceptibility to SLE[16], Clarkson
disease[19] and SS[20]. In our study, we analysed the rs3130983, rs3778638 and rs4959053 gene which had been investigated in above researches. We found a significant association of genotypes in rs3778638 of PSORS1C1 with AITD. Simultaneously, a tendency of stronger association of genotypes in rs3778638 with GD subsets was also observed. And in AITD and GD patients, separately, it is clear that the frequencies of AG genotype of rs3778638, were significantly lower than their control groups. The AG genotype showed protective influence for AITD and GD.

IL-23/IL-17 axis, as one of the critical immune-related genes, has made contribute to psoriasis susceptibility. In psoriasis, IL-23-induced and IL-17-mediated inflammatory responses showed a pivotal role [26]. IL17 overexpression in AITD was also showed in many studies[27–29]. To the study of single-nucleotide polymorphism (SNP) data have confirmed that IL17 gene polymorphisms may affect the susceptibility to AITD[12]. Combined with the results of these studies, PSORS1C1 gene may be involved in the pathogenesis of AITD by influencing the secretion of IL17, though the function of PSORS1C1 gene is not yet known.

AITD is a complex disease, its etiology contains both susceptibility genes and environmental factors. Candidate gene analysis, whole genome screening and other various techniques have been used to identify the genes contributing to the etiology of AITD. Genome-wide association studies (GWAS) in the past decade have facilitated screening of a greater proportion of the genome. But AITD susceptibility genes are still not identified. PSORS1C1 was confirmed as a susceptibility gene of immune system diseases, and has been identified the influence in several diseases. Thus, we thought it prudent to determine the frequencies of these polymorphisms in AITD subjects. Our study fills the vacancy in this field. And our present study has observed the correlation between PSORS1C1 SNPs and AITD in a Chinese Han population. These results suggest that PSORS1C1 might affect the immune system and play an important role in the development of AITD.

Conclusions
In summary, these data confirmed the influence of PSORS1C1 gene on a susceptibility to AITDs in a Chinese population. It indicated that the PSORS1C1 gene could be a risk gene of AITD. And it also provided evidence to reinforce this locus as a common autoimmunity risk factor.
Abbreviations
GD: Graves' disease
HT: Hashimoto's thyroiditis,
PSORS1C1: psoriasis susceptibility 1 candidate 1
SNP: single nucleotide polymorphism

Declarations

Availability of data and materials
All data generated or analysed during this study are included in this published article. Additional data are however available from the authors upon reasonable request.

Acknowledgements
The authors would like to thank all of the participants in the study.

Funding
This work was supported by the National Natural Science Foundation of China (No. 81670722, 81873636); Shanghai Natural Science Foundation(No.18ZR1433800) and Shanghai Medical Key Specialty(No.ZK2019C09).

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Contribution
Yanfei Jiang wrote the main part of the manuscript and took part in the planning and execution of the experiments. Ronghua Song took part in the development of the model, planned and carried out the main part of the experiments, analyzed the results and assisted in the mass transfer experiments.
Jinan Zhang participated in the coordination of the study and reviewed the manuscript. All authors read and approved the final manuscript. All the authors participated in the experimental design, sample collection, sample extraction, and data analysis.

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**Competing interests**

The authors declare no financial or commercial conflict of interest.

**Ethics declarations**

Ethics approval and consent to participate

Written informed consent was obtained from all of the adult participants and the guardians of participants under 18 years old. The present study was approved by the Ethics Committees of the Jinshan Hospital of Fudan University (Shanghai, China).

**Consent for publication**

Written informed consent for publication of clinical details and clinical images was obtained from all of the adult participants and the legal guardians of any participant under the age of 18.

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Figures

![Figure 1](image-url)

**Figure 1**

PSORS1C1 LD block in the Haploview 4.2