Association of single-nucleotide polymorphisms in the STAT3 gene with autoimmune thyroid disease in Chinese individuals

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Received: 20 May 2013 / Revised: 19 August 2013 / Accepted: 10 September 2013 / Published online: 1 October 2013
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Abstract

The aim of this study was to investigate the association between signal transducer and activator of transcription 3 (STAT3) polymorphisms and autoimmune thyroid diseases and clinical features. We genotyped six single-nucleotide polymorphisms (SNPs) rs1053005, rs2293152, rs744166, rs17593222, rs2291281, and rs2291282 of STAT3 gene in 667 patients with autoimmune thyroid disease (417 Graves’ disease (GD) and 250 Hashimoto’s thyroiditis (HT)) and 301 healthy controls. The allele A from rs1053005 was significantly less frequent in both GD and HT patients (P=0.0024, OR=0.6958, 95% CI=0.5508–0.8788; P=0.0091, OR=0.7013, 95% CI=0.5397–0.9112, respectively). The AA genotype of rs1053005 was less in GD and HT patients too (P=0.0025, OR=0.6278, 95% CI=0.466–0.847) and (P=0.0036, OR=0.601, 95% CI=0.428–0.843). The allele G from rs17593222 increased the susceptibility to the ophthalmopathy development both in autoimmune thyroid disease (AITD) and GD patients (P=0.0007, OR=3.980, 95% CI=1.871–8.464; P=0.0081, OR=3.378, 95% CI=1.441–7.919, respectively). The allele A and AA genotype of SNP rs1053005 may protect individuals from the susceptibility toAITD and their frequency decreased in AITD patients. In addition, the allele G of rs17593222 may increase the ophthalmopathy risk in AITD patients. Our findings suggest the existence of association between STAT3 gene and AITD, thus adding STAT3 gene to the list of the predisposing genes to AITD.

Keywords Signal transducer and activator of transcription 3 (STAT3) · Single-nucleotide polymorphisms (SNPs) · Autoimmune thyroid disease · Graves’ disease · Hashimoto’s thyroiditis

Introduction

Autoimmune thyroid diseases (AITDs), including Graves’ disease (GD) and Hashimoto’s thyroiditis (HT), are among the most common human autoimmune diseases. The prevalence in Caucasians is 1% (Hollowell et al. 2002). GD is characterized clinically by hyperthyroidism, diffuse goiter, and the presence of thyroid peroxidase antibodies, and HT is characterized by apoptosis of thyrocytes leading to hypothyroidism and the presence of thyroid peroxidase antibodies (TPOAb) or antibodies against thyroglobulin (TGAb). Despite their contrasting clinical presentations, GD and HT share many common features, mainly the infiltration of the thyroid by T cells and the production of anti-thyroid autoantibodies (Tomer 1997). The pathogenesis for AITDs remains unclear, though it is thought to involve several risk factors, including genetic risk factors (Tomer and Davies 2003) and environmental triggers such as cigarette smoking, iodine intake, and infection (Tomer and Davies 1993).

T helper cells are a group of immune cells that mediate adaptive immunity in vertebrates and are comprised of four major subtypes, Th1, Th2, Th17, and Treg (Dong 2008; Egwuagu 2009; Korn et al. 2009). In comparison to other T helper subsets, IL-17-producing T cells (Th17) are present in very low amounts in human blood but become highly elevated during chronic inflammation and are implicated in the pathology...
of several autoimmune diseases and chronic inflammatory disorders (Amadi-Obi et al. 2007). Recently, one of our studies identified the association of interleukin-17A and interleukin-17F gene single-nucleotide polymorphisms with autoimmune thyroid diseases. IL-17F/rs763780 polymorphisms may affect the susceptibility to AITD, and IL-17A/rs3819025 SNP is likely a protective factor to GD in the Chinese population (Yan et al. 2012). IL-17A and IL-17F are two IL-17 cytokine family members responsible for the pathogenic activity of the Th17 cells (Rutitzky et al. 2005). The differentiation of naive CD4+ T cells toward the Th17 developmental pathway is mediated through activation of STAT3 pathways and Th17 lineage-specific transcription factors (Ivanov et al. 2007; Yang et al. 2007; Dong 2008; Korn et al. 2009). IL-6, IL-21, and IL-23 are all cytokines that activate the transcription factor STAT3 (Chen et al. 2007). Loss of STAT3 expression abrogates Th17 differentiation and inhibits the production of cytokines secreted by Th17 cells (Ivanov et al. 2007).

STAT3 gene polymorphisms had been reported to be associated with several immune diseases, including Crohn’s disease (CD) (Ferguson et al. 2010), type1 diabetes mellitus (Fung et al. 2009), Sjogren’s syndrome (Okuma et al. 2013), and psoriatic arthritis (PsA) (Cenit et al. 2013). No reports about STAT3 SNPs’ correlation to AITDs had been seen.

In this study, we attempted to find the association of SNPs rs1053005, rs2293152, rs744166, rs17593222, rs2291281, and rs2291282 at the STAT3 gene locus with GD and HT in a Han Chinese population.

Materials and methods

Subjects

All AITD (GD and HT) patients in the present case–control study were recruited from the Department of Endocrinology, the First Affiliated Hospital of Xi’an Jiaotong University. The diagnostic criteria for GD were mainly determined by clinical manifestation and laboratory biochemical proof of hyperthyroidism and the presence of diffuse goiter, the positive circulating TSH receptor antibody (TRAb) and antibody against thyroglobulin (TgAb) or antibody against thyroid peroxidase (TPOAb). HT was defined on the basis of enlarged thyroid and the high level of either TPOAb or TgAb, with or without clinical and biochemical hypothyroidism. Fine needle aspiration was performed for any demonstrative and suspected cases of hypothyroidism. Three hundred and one healthy controls were recruited from unrelated physical examination individuals in the Health Check-up Center of the same hospital, with thyroid disease and other autoimmune diseases ruled out. All the subjects, including AITD patients and controls, were Han Chinese and signed the informed consent. The research project was approved by the Ethics Committee of the First Affiliated Hospital of Medical School of Xi’an Jiaotong University. As shown in Table 1, our study investigated 667 AITD patients, who comprised 417 GD (124 men and 293 women) and 250 HT patients (39 men and 211 women). In GD patients, the average onset age was 32.31±14.07, 72 individuals had family history and 98 had ophthalmopathy. In HT patients, the average onset age was 30.29±13.05, 54 individuals had family history and 6 had ophthalmopathy.

Genotyping

Peripheral venous blood of 2 ml from the subjects was collected in an EDTA tube. The genomic DNA was extracted by salting-out method, using RelaxGene Blood DNA System (TIANGEN BIOTECH, Beijing, China), according to the manufacturers’ protocol. Genotyping of SNPs (rs1053005, rs2293152, rs744166, rs17593222, rs22912821, and rs2291282) was performed by MassARRAY system (Sequenom, San Diego, CA, USA) using the chip-based matrix-assisted laser desorption ionization time-of-flight mass spectrometry technology (Du et al. 2011). This is a well-selected platform by many researchers during studies including SNP genotyping. It has high specificity and sensitivity (Xiu-Cheng Fan et al. 2008). Primers were obtained from Sangon Biotech (Shanghai, China). Briefly, multiplex reaction was designed using Assay Designer software version 3.0 (Sequenom) and was processed following standard protocols for iPLEX chemistry. The reaction products were then cleaned and dispensed onto a SpectroCHIP bioarray. The chip was scanned using MassARRAY workstation version 3.3, and the resulting spectra were analyzed using the Sequenom TYPER software.

| Table 1  | Clinical data of AITD patients and controls |
|----------|------------------------------------------|
|          | GD  | HT    | Control |
| Number   | 417 | 250   | 301     |
| Gender   |     |       |         |
| Female   | 293 | 211   | 210     |
| Male     | 124 | 39    | 91      |
| Age      |     | 34.48±13.95 | 31.9±13.1 | 33.5±12.59 |
| Onset of age | 32.31±14.07 | 30.29±13.05 |
| Thyroid size |     |       |         |
| Normal   | 85  | 41    |         |
| I        | 35  | 17    |         |
| II       | 231 | 169   |         |
| III      | 66  | 23    |         |
| Family history |     |       |         |
| (+)      | 72  | 54    |         |
| (-)      | 345 | 196   |         |
| Ophthalmopathy |     |       |         |
| (+)      | 98  | 6     |         |
| (-)      | 319 | 244   |         |
Clinical phenotype analysis

Patients’ clinical characteristics data were presented in Table 1. We conducted investigation in autoimmune thyroid patients (GD and HT) and their clinical features subphenotypes. Association analyses between genotypes and clinical manifestations of GD or HT were separately investigated involving (1) presence or absence of AITD family history (defined as the subjects’ first-degree relatives including parents, children, and siblings or second-degree relatives such as grandparents, uncles, and aunts who had AITD occurrence); (2) presence or absence of ophthalmopathy (defined as a distinctive disorder characterized by inflammation and swelling of the extraocular muscles and orbital fat, eyelid retraction, periorbital edema, episcleral vascular injection, conjunctive swelling, and proptosis).

Statistical analysis

The clinical data are expressed as $M \pm SD$. All SNPs were analyzed using HapLoView 4.2 software to perform Hardy-Weinberg equilibrium (HWE) tests. Haplotype blocks were generated using the default algorithm based on methods established by Gabriel et al. (2002). Because all SNPs studied here were not located in the same block (data not shown), we did no haplotype frequency calculation and linkage disequilibrium (LD) test. Allele and genotype frequencies between cases and controls were computed by chi square test or Fisher’s exact test. Differences between groups were determined by the odds ratio (OR) and 95 % confidence interval (95 %CI). All statistical analyses were performed using the software GraphPad Prism 5. A $p$ value less than 0.05 was considered significant.

Results

Allele and genotype results

All of these six SNPs in both case and control groups were in HWE ($p > 0.05$). Table 2 shows the allele and

**Table 2** Allele and genotype frequencies in AITD patients and controls

| SNP         | Alleles | Con (%) | CD (%) | $P$  | OR          | 95%CI          | HT (%) | $P$  | OR          | 95%CI          |
|-------------|---------|---------|--------|------|-------------|----------------|--------|------|-------------|----------------|
| rs1053005   | G       | 153 (25.5) | 275 (32.97) | 0.0024 | 0.6958     | 0.5508–0.8788 | 164 (32.8) | 0.0091 | 0.7013     | 0.5397–0.9112 |
|             | A       | 447 (74.5)  | 559 (67.03)  |       |             |                | 336 (67.2)  |        |             |                |
|             | AA      | 170 (56.67) | 188 (45.08)  | 0.008 |             |                | 110 (44)    | 0.0125 |             |                |
|             | AG      | 107 (35.67) | 183 (43.88)  |       |             |                | 116 (46.4)  |        |             |                |
|             | GG      | 23 (7.66)   | 46 (11.04)   |       |             |                | 24 (9.6)    |        |             |                |
| rs17593222  | C       | 586 (97.67) | 810 (97.36)  | 0.7363 |             |                | 493 (98.6)  | 0.279  |             |                |
|             | G       | 14 (2.33)   | 22 (2.64)    |       |             |                | 7 (1.4)     |        |             |                |
|             | CC      | 286 (95.33) | 394 (94.71)  | 0.7329 |             |                | 243 (97.2)  | 0.2744 |             |                |
|             | CG      | 14 (4.67)   | 22 (5.29)    |       |             |                | 7 (2.8)     |        |             |                |
| rs2291281   | A       | 8 (1.33)    | 6 (0.72)     | 0.2821 |             |                | 6 (1.2)     |        |             |                |
|             | G       | 592 (98.67) | 828 (99.28)  |       |             |                | 492 (98.8)  |        |             |                |
|             | AG      | 8 (2.67)    | 6 (1.44)     | 0.2799 |             |                | 6 (2.41)    |        |             |                |
|             | GG      | 292 (97.33) | 411 (98.56)  |       |             |                | 243 (97.59) |        |             |                |
| rs2291282   | C       | 7 (1.17)    | 17 (2.04)    | 0.2194 |             |                | 4 (0.8)     | 0.7627 |             |                |
|             | T       | 593 (98.83) | 817 (97.96)  |       |             |                | 496 (99.2)  |        |             |                |
|             | CT      | 7 (2.33)    | 17 (4.08)    | 0.2156 |             |                | 4 (1.6)     | 0.7615 |             |                |
|             | TT      | 293 (97.67) | 400 (95.92)  |       |             |                | 246 (98.4)  |        |             |                |
| rs2293152   | C       | 293 (49)    | 371 (44.7)   | 0.1189 |             |                | 234 (46.99) | 0.5438 |             |                |
|             | G       | 305 (51)    | 459 (55.3)   |       |             |                | 264 (53.01) |        |             |                |
|             | CC      | 68 (22.74)  | 79 (19.04)   | 0.2577 |             |                | 53 (21.29)  | 0.7764 |             |                |
|             | CG      | 157 (52.51) | 213 (51.33)  |       |             |                | 128 (51.41) |        |             |                |
|             | 66      | 74 (24.75)  | 123 (29.63)  |       |             |                | 68 (27.3)   |        |             |                |
| rs744166    | C       | 203 (34.06) | 161 (38.15)  | 0.1849 |             |                | 199 (39.8)  | 0.0513 |             |                |
|             | T       | 393 (65.94) | 261 (61.85)  |       |             |                | 301 (60.2)  |        |             |                |
|             | CC      | 34 (11.41)  | 22 (10.43)   | 0.0704 |             |                | 41 (16.4)   | 0.1381 |             |                |
|             | CT      | 135 (45.3)  | 117 (55.45)  |       |             |                | 117 (46.8)  |        |             |                |
|             | TT      | 129 (43.29) | 72 (34.12)   |       |             |                | 92 (36.8)   |        |             |                |
genotype frequencies and case–control association analysis for each SNP. In rs1053005, we found that allele A was significantly less frequent in GD and HT patients than in controls ($p=0.0024$, OR=0.6958, 95%CI=0.5508–0.8788) and ($p=0.0091$, OR=0.7013, 95%CI=0.5397–0.9112) (shown in Table 2). Also, AA genotype of rs1053005 was less in GD ($p=0.0025$, OR=0.6278, 95%CI=0.466–0.847) and HT ($p=0.0036$, OR=0.601, 95%CI=0.428–0.843) patients than the control, which evidently indicated the AA genotype could decrease the susceptibility to GD and HT (shown in Table 3). SNP rs744166 showed a marginal significant trend between HT subjects and control group ($p=0.0513$) (shown in Table 2), while the distribution of TT genotype from rs744166 ($p=0.0429$, OR=0.6786, 95%CI=0.471–0.978) was decreased in GD patients compared to the healthy controls (shown in Table 3). Nevertheless, we did not find any significant difference both in genotype and allele frequencies between patients and controls either in rs17593222, rs2293152, or in rs2293152 SNPs.

**Table 3** Genotype distributions of rs1053005 and rs744166 in AITD patients and controls

| SNP      | Genotype | Con (%) | GD (%) | $P$     | OR    | CI       | HT (%) | $P$     | OR    | CI       |
|----------|----------|---------|--------|---------|-------|---------|--------|---------|-------|---------|
| rs1053005| AG+GG    | 130 (43.33) | 229 (54.92) | 0.0025  | 0.6278 | 0.466–0.847 | 140 (56) | 0.0036  | 0.601 | 0.428–0.843 |
|          | AA       | 170 (56.67)   | 188 (45.08)  |         |       |         |        |         |       |         |
| rs744166 | CT+CC    | 169 (56.71)   | 139 (65.88)  | 0.0429  | 0.6786 | 0.471–0.978 | 158 (63.2) | 0.1374  |       |         |
|          | TT       | 129 (43.29)   | 72 (34.12)   |         |       |         |        |         |       |         |

Genotype and clinical phenotype associations

When we further compared the SNP rs1053005 between patients with and those without family history, in both GD and HT patients, no significant difference was observed (data not shown).

Four SNPs, including rs1053005, rs17593222, rs2293152, and rs744166, showed a significant association when ophthalmopathy AITD patients were compared to the healthy controls (shown in Table 4). Only two SNPs (rs1053005 and rs744166) in non-ophthalmopathy AITD patients showed difference when compared to the controls (shown in Table 4). When we compared the ophthalmopathy to the non-ophthalmopathy within AITD patients, SNP rs17593222 showed significant association ($p=0.0007$, OR=3.980, 95%CI=1.871–8.464).

Graves’ ophthalmopathy (GO) also known as thyroid-associated ophthalmopathy is a condition that primarily affects the extraocular muscles, the muscles that rotate the eyeball up, down, and to the sides. It can happen

**Table 4** The allele and genotype frequencies of rs1053005, rs17953222, rs2293152, and rs744166 in ophthalmopathy and non-ophthalmopathy patients and controls

| SNP      | Alleles | Con (%) | Ophthalmopathy | $P$     | OR    | CI       | Non-ophthalmopathy | $P$     | OR    | CI       |
|----------|---------|---------|----------------|---------|-------|---------|---------------------|---------|-------|---------|
| rs1053005| A       | 447 (74.5) | 140 (67.31)   | 0.0475  | 1.419 | 1.007–2.000 | 753 (66.99) | 0.0012  | 1.439 | 1.153–1.797 |
|          | G       | 153 (25.5)  | 68 (32.69)   |         |       |         | 371 (33.01) |         |       |         |
|          | AA      | 170 (56.67) | 48 (46.15)   | 0.0685  |       |         | 249 (44.31) |         |       |         |
|          | AG+GG   | 130 (43.33) | 56 (53.85)   |         |       |         | 313 (55.69) |         |       |         |
| rs17593222| C      | 586 (97.67) | 196 (94.23)  | 0.0218  | 2.563 | 1.165–5.635 | 1105 (98.48) | 0.2545  |       |         |
|          | G       | 19 (2.33)   | 12 (5.77)    |         |       |         | 17 (1.52)   |         |       |         |
|          | CC      | 286 (95.33) | 92 (88.46)   | 0.0197  | 2.665 | 190–5.967 | 544 (96.97) | 0.2502  |       |         |
|          | CG      | 14 (4.67)   | 12 (11.54)   |         |       |         | 17 (3.03)   |         |       |         |
| rs2293152| C       | 305 (51)   | 79 (37.98)   | 0.0061  | 1.569 | 1.136–2.166 | 521 (46.60) | 0.3612  |       |         |
|          | G       | 30 (49)    | 129 (62.02)  |         |       |         | 597 (53.40) |         |       |         |
|          | GG      | 74 (24.75)  | 44 (42.31)   | 0.0011  | 0.4485 | 0.280–0.717 | 150 (26.83) | 0.5681  |       |         |
|          | CG+CC   | 225 (75.25) | 60 (57.69)   |         |       |         | 409 (73.17) |         |       |         |
| rs744166 | C       | 203 (34.06) | 87 (42.23)   | 0.0433  | 0.7065 | 0.511–0.977 | 444 (39.57) | 0.0280  | 0.7888 | 0.641–0.971 |
|          | T       | 393 (65.94) | 119 (57.77)  |         |       |         | 678 (60.43) |         |       |         |
|          | CC      | 34 (11.41)  | 20 (19.42)   | 0.0454  | 0.5345 | 0.292–0.979 | 87 (15.51) | 0.7017  |       |         |
|          | CT+TT   | 264 (88.59) | 83 (80.58)   |         |       |         | 474 (84.49) |         |       |         |
not only in GD but also in HT patients. Nevertheless, we can see GD contributed much more to the development of ophthalmopathy as shown in the Table 5.

Allele G from rs17593222 also increased the risk of ophthalmopathy ($p=0.0081$, OR=3.378, 95%CI=1.441–7.919) within GD patients. The minor allele C from rs17593222 increased the susceptibility to the ophthalmopathy development both in AITD and GD patient subgroups (shown in Tables 6 and 7). CG genotype of rs17593222 SNP increased the risk of ophthalmopathy too when compared to CC genotype ($p=0.0073$, OR=3.529, 95%CI=1.480–8.416). GG genotype from SNP rs2293152 also increased the risk of ophthalmopathy in GD patients ($p=0.031$, OR=1.729, 95%CI=1.073–2.784) (shown in Table 7). No differences were seen in other SNPs, including rs1053005 and rs744166 (data not shown).

Discussion

STAT3 gene is located on chromosome17q21.31. The protein encoded by this gene is a member of the STAT protein family. In response to cytokines and growth factors, STAT family members are phosphorylated by the receptor-associated kinases and then form homo- or heterodimers that translocate to the cell nucleus where they act as transcription activators (Zhong et al. 1994). This protein is activated through phosphorylation in response to various cytokines and growth factors including IFNs, EGF, IL5, IL6, HGF, LIF, and BMP2. It mediates the expression of many genes in response to cell stimuli and thus plays a key role in many cellular processes such as cell growth and apoptosis. STAT3 also plays key roles in Th17 lymphocyte development and differentiation.

SNPs rs744166, rs2293152, and rs1053005 had been found to be associated with many autoimmune diseases. The association with psoriatic arthritis (PsA) in SNP rs744166 was observed in Spanish Caucasian origin (Cenit et al. 2013). So did its association with ankylosing spondylitis (AS) in white European ancestry (Danoy et al. 2010) and that with multiple sclerosis (MS) in Finland population (Jakkula et al. 2010). The susceptibility of STAT3 rs744166 TT homozygotes for ulcerative colitis (UC) was found in Hungarian (Polgar et al. 2012). Also, the association of rs744166 to Crohn’s disease (CD) was also confirmed in adult German (Prager et al. 2012). STAT3 (rs2293152, rs1053005) were significantly associated with AS in Han Chinese (Davidson et al. 2011). A significantly increased frequency of the GG genotype of the STAT3 rs2293152 was also observed in patients with BD in the Han Chinese population (Hu et al. 2012). The frequencies of a C allele and its homozygous CC genotype at rs2293152 SNP in STAT3 in CD patients were significantly higher than those in control subjects in the Japanese population (Sato et al. 2009). However, no study about the STAT3 SNPs association with AITDs was reported until now.

Our study examined the association between six SNPs of STAT3 gene and AITD in a Chinese Han population. Regarding the allele frequencies and genotype analysis of STAT3, we found that rs1053005 major allele A was significantly decreased in GD and HT patients and lowered the risk

Table 5 Ophthalmopathy in AITD disease

|       | Ophthalmopathy (%) | Non-ophthalmopathy (%) | P     | OR   | CI      |
|-------|-------------------|------------------------|-------|------|---------|
| GD    | 98 (94.23)        | 319 (56.76)            | <0.0001 | 12.44 | 5.365–28.86 |
| HT    | 6 (5.77)          | 243 (43.24)            |       |      |         |

Table 6 The allele and genotype frequencies of rs17593222 and rs2293152 in ophthalmopathy and non-ophthalmopathy AITD patients

| SNP     | Alleles | Non-ophthalmopathy (%) | Ophthalmopathy (%) | P     | OR   | CI      |
|---------|---------|------------------------|-------------------|-------|------|---------|
| rs17593222 | C       | 1105 (98.48)           | 196 (94.23)       | 0.0007 | 3.980 | 1.871–8.464 |
|         | G       | 17 (1.52)              | 12 (5.77)         |       |      |         |
|         | CC      | 544 (96.97)            | 92 (88.46)        | 0.0006 | 4.174 | 1.930–9.028 |
|         | CG      | 17 (3.03)              | 12 (11.54)        |       |      |         |
| rs2293152 | C       | 521 (46.60)            | 82 (39.42)        | 0.0583 |      |         |
|         | G       | 597 (53.40)            | 126 (60.58)       |       |      |         |
|         | CG+CC   | 409 (73.17)            | 63 (39.42)        | 0.0129 | 1.774 | 1.148–2.743 |
|         | GG      | 150 (26.83)            | 41 (39.42)        |       |      |         |
of diseases by 30.42 and 29.87 %, respectively. The AA genotype frequencies in control, GD, and HT collections were 56.67, 45.08, and 44 %, respectively. There is a clear observation that the AA could lower the risk of GD or HT by 37.22 and 39.9 %, respectively, and protect individuals from developing AITDs. SNP rs744166 showed a marginal difference between the HT and control groups (p =0.0513). We observed much higher risk of ophthalmopathy development both in AITD and GD group with G allele of rs17593222 (OR=3.980 and 3.378, respectively).

Dysregulation of effector T cell responses represents a common feature of a wide range of autoimmune diseases. Activated CD4+ T cells differentiate into distinct functional subsets, characterized by heritable patterns of cytokine secretion and the expression of specific transcription factors. IL-17 is mostly known for its pro-inflammatory activities, both in vitro and in vivo, and its expression is increased in inflammatory tissues (Kolls and Linden 2004). One of these subsets, CD4+ T cells that preferentially produce IL-17, designed Th17, have attracted tremendous attention because of the connection with autoimmune disease (Stockinger and Veldhoen 2007; Weaver et al. 2007; Miossec et al. 2009). An increasing body of evidence shows the requirement of STAT3 for Th17 cell development. Patients suffering from autosomal dominant hyper-IgE syndrome, associated with negative mutations in STAT3, had impaired Th17 cell differentiation (de Beaucoudrey et al. 2008; Ma et al. 2008; Milner et al. 2008; Renner et al. 2008).

STAT3 bound to and regulated multiple genes that contribute to the Th17 phenotype, including not only the IL17 locus itself, IL21, and IL23r but also CCR6 (Durant et al. 2010; Ghoreschi et al. 2010; Yang et al. 2011). STAT3 also bound to genes encoding transcription factors critical for Th17 differentiation including Rorc (which encodes Rorγt), Irf4, Batf, and Nfibiz (Durant et al. 2010).

We and other researchers have found that there is an increased differentiation of Th17 lymphocytes and an enhanced synthesis of Th17 cytokines in AITDs. These may substantially contribute to the pathogenesis of thyroid autoimmunity (Figueroa-Vega et al. 2010; Qin et al. 2012). Our previous work had also found the association of IL-17A and IL-17F SNPs with AITDs, which were two IL-17 cytokine family members secreted by Th17 cells (Yan et al. 2012).

Immunohistochemical analysis had demonstrated differential expression patterns of the various members of the STAT transcription factors in lymphocytic thyroiditis, indicating that each member of this conserved protein family has its distinct functions in the development of the disease. The cell-type-specific expression patterns of STAT proteins in human lymphocytic thyroiditis reflect their distinct and partially antagonistic roles in orchestrating the balance between degenerating and regenerating processes within a changing cytokine environment (Staab et al. 2012). STAT protein members have different effect on Th17 differentiation and may contribute to their roles in human lymphocytic thyroiditis pathogenesis.

STAT3 is a key signaling molecule within the Th17 lymphocyte differentiation pathway. It may play roles in AITDs and ophthalmopathy development by regulating Th17 lymphocyte differentiation. Here, we report the contribution of STAT3 SNPs to AITDs and ophthalmopathy susceptibility in patients for the first time. The AITDs occurrence may be attributed to altered differentiation of Th17 lymphocytes and different synthesis of Th17 cytokines in the tissue.

Acknowledgments This project was supported by grants from the National Natural Science Foundation of China (30871184, 81070627).

Conflict of interest The authors declare no competing interest. The authors alone are responsible for the content and writing of the paper.

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