Association of TNFAIP3 interacting protein 1, TNIP1 with systemic lupus erythematosus in a Japanese population: a case-control association study

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Abstract

Introduction: TNFAIP3 interacting protein 1, TNIP1 (ABIN-1) is involved in inhibition of nuclear factor-κB (NF-κB) activation by interacting with TNF alpha-induced protein 3, A20 (TNFAIP3), an established susceptibility gene to systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). Recent genome-wide association studies revealed association of TNIP1 with SLE in the Caucasian and Chinese populations. In this study, we investigated whether the association of TNIP1 with SLE was replicated in a Japanese population. In addition, association of TNIP1 with RA was also examined.

Methods: A case-control association study was conducted on the TNIP1 single nucleotide polymorphism (SNP) rs7708392 in 364 Japanese SLE patients, 553 RA patients and 513 healthy controls.

Results: Association of TNIP1 rs7708392C was replicated in Japanese SLE (allele frequency in SLE: 76.5%, control: 69.9%, \( P = 0.0022 \), odds ratio [OR] 1.40, 95% confidence interval [CI] 1.13-1.74). Notably, the risk allele frequency in the healthy controls was considerably greater in Japanese (69.9%) than in Caucasians (24.3%). A tendency of stronger association was observed in the SLE patients with renal disorder (\( P = 0.00065 \), OR 1.60 [95%CI 1.22-2.10]) than in all SLE patients (\( P = 0.0022 \), OR 1.40 [95%CI 1.13-1.74]). Significant association with RA was not observed, regardless of the carriage of human leukocyte antigen DRβ1 (HLA-DRB1) shared epitope. Significant gene-gene interaction between TNIP1 and TNFAIP3 was detected neither in SLE nor RA.

Conclusions: Association of TNIP1 with SLE was confirmed in a Japanese population. TNIP1 is a shared SLE susceptibility gene in the Caucasian and Asian populations, but the genetic contribution appeared to be greater in the Japanese and Chinese populations because of the higher risk allele frequency. Taken together with the association of TNFAIP3, these observations underscore the crucial role of NF-κB regulation in the pathogenesis of SLE.

Introduction

TNFAIP3 (tumor necrosis factor α-induced protein 3) encodes a ubiquitin-editing protein, A20, known as an inhibitor of nuclear factor-κB (NF-κB). Several adaptor molecules are thought to associate with A20 and be involved in inhibition of NF-κB [1]. TNIP1 (TNFAIP3 interacting protein 1), also known as ABIN (A20-binding inhibitor of NF-κB)-1, is one such adaptor molecule binding to A20. TNIP1 mRNA is strongly expressed in peripheral blood lymphocytes, spleen and skeletal muscle, and the expression is also detected in kidney [2]. TNIP1 expression is induced by NF-κB, and in turn, overexpression of TNIP1 inhibits NF-κB activation by TNF [1], although deficiency of TNIP1 has few effects on NF-κB inhibition [3]. Thus, TNIP1 appears to play a
role in NF-κB inhibition, at least partly by interacting with A20. In addition, TNIP1 was shown to inhibit TNF-induced apoptosis independently of A20 [3].

TNFAIP3, located at 6q23, has been identified as a susceptibility gene for both systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) in Caucasian and Asian populations [4-8]. Recently, Shimane et al. [9] replicated association of TNFAIP3 single nucleotide polymorphisms (SNPs) with SLE and RA in a Japanese population. We also detected association of TNFAIP3 rs2230926 with Japanese SLE patients in an independent study [10].

Recently, a genome-wide association study (GWAS) reported association of TNIP1 (5q32-q33.1) as well as TNFAIP3 SNPs with psoriasis in the Caucasian populations [11]. Subsequently, two recent GWAS revealed association of TNIP1 intronic SNPs rs7708392 and rs10036748, which are in strong linkage disequilibrium (LD) with SLE in the Caucasian (European-American and Swedish) and Chinese Han populations, respectively [8,12]. These observations underscored the role of the pathway involving TNFAIP3-TNIP1 in the genetic predisposition to SLE. The association of TNIP1 with SLE needs to be further confirmed.

Recently, it has become increasingly clear that SLE and RA share a number of susceptibility genes. TNFAIP3 [4-10], STAT4 [13,14] and BLK [15,16] represent such shared susceptibility genes. TNIP1 has been shown to be upregulated in synovial tissues from RA [17], raising a possibility that TNIP1 may also play a role in the pathogenesis of RA. To date, association of RA with TNPI1 has not been reported.

This study was conducted to examine whether TNIP1 was associated with SLE and RA in a Japanese population.

Materials and methods
Patients and controls
Three hundred sixty-four Japanese patients with SLE (21 males and 343 females, mean ± SD age, 42.8 ± 13.9 years), 553 patients with RA (43 males and 510 females, mean ± SD age, 58.0 ± 11.3 years) and 513 healthy controls (238 males and 275 females, mean ± SD age, 34.1 ± 9.9 years) were recruited. The patients with SLE and healthy controls were stratified by the presence or absence of human leukocyte antigen DR [1 (HLA-DRB1)] shared epitope. The numbers of the missing data were 6 (RA) and 15 (controls).

The control group consisted of healthy volunteers without any signs or symptoms of autoimmune diseases recruited at the same institutes.

This study was carried out in compliance with the Helsinki Declaration. The study was reviewed and approved by the research ethics committees of the University of Tsukuba, Sagamihara National Hospital and Juntendo University. Informed consent was obtained from all study participants.

Genotyping
Genotyping of TNIP1 rs7708392 was carried out using the TaqMan genotyping assay (Applied Biosystems, Foster City, CA, USA), according to the manufacturer’s instructions, using a TaqMan probe C_29349759_10. HLA-DRB1 was genotyped at the sequence level using a polymerase chain reaction (PCR) microtiter plate hybridization assay as previously described [20].

Statistical analysis
A case control association study was conducted by χ² test using 2 × 2 contingency tables. The null hypotheses tested in this study were that there was no difference in the genotype or allele frequencies between all SLE patients and healthy controls, between SLE subsets and healthy controls, between all RA patients and all healthy controls, or between RA patients and healthy controls stratified by the presence or absence of HLA-DRB1 shared epitope.

The power to detect association was calculated on the basis of the frequency of the rs7708392C allele in Japanese healthy controls (69.9%). The sample size of this study (364 SLE patients, 553 RA patients and 513 controls) had the power of 80% to detect association when the genotype relative risk was 1.36 (SLE) and 1.32 (RA) or greater, respectively [21].

To adjust for the gender difference between patients and healthy controls (Table 1), multiple logistic

Table 1 Characteristics of the patients and healthy controls studied

|               | SLE  | RA    | Healthy controls |
|---------------|------|-------|------------------|
| n             | 364  | 553   | 513              |
| Male/female   | 21/343 | 43/510 | 238/275          |
| Age*          | 42.8 ± 13.9 | 58.0 ± 11.3 | 34.1 ± 9.9       |

*Mean ± SD.
regression analyses were employed. The following were used as independent variables: for the genotypes of rs7708392, C/C = 1, C/G = 0, G/G = 0 under the recessive model for the C allele, C/C = 2, C/G = 1, G/G = 0 under the codominant model, and for gender, male = 0, female = 1.

The interaction between TNIP1 rs7708392 and TNFAIP3 rs2230926, which we recently replicated to be associated with SLE [10], was examined in 308 SLE, 372 RA and 449 healthy controls, using logistic regression analysis. Codominant (risk allele homozygotes $x_i = 2$, heterozygotes $x_i = 1$, nonrisk allele homozygotes $x_i = 0$), dominant (risk allele homozygotes $x_i = 1$, heterozygotes $x_i = 1$, nonrisk allele homozygotes $x_i = 0$) and recessive (risk allele homozygotes $x_i = 1$, heterozygotes $x_i = 0$, nonrisk allele homozygotes $x_i = 0$) models for gene $i$ were tested. The logistic regression model for interaction between gene $i$ and gene $j$ was given by $\logit(P) = \beta_0 + \beta_ix_i + \beta_jx_j + \beta_{ijx_ix_j}$. The deviation from 0 was evaluated for $b_{ij}$ by the Wald test. Population attributable risk percentage (PAR%) was estimated by the formula:

$$\text{PAR}\% = \frac{P_e(\text{RR} - 1)/(P_e(\text{RR} - 1) + 1) \times 100,}{\text{PAR}\%}$$

where $P_e$ represents the risk genotype frequency in the population and $\text{RR}$ represents the relative risk of the risk genotype [22]. Although $\text{RR}$ cannot be determined from the case-control study design, it can be approximated by odds ratio (OR) when the incidence of the disease is sufficiently low. Because the incidence of SLE has been reported to be 3.0 in Japan and 1.8-7.6 in the United States per 100,000 persons per year [23] and is sufficiently small, OR can be adequately used for an approximation for $\text{RR}$. The PAR% in the Caucasian populations were calculated using the raw genotype count data for the previously reported study (cases: C/C 293, C/G 1389, G/G 1632, controls: C/C 735, C/G 4510, G/G 7050) [12].

**Results**

**Replication of TNIP1 association with SLE in Japanese**

The association of TNIP1 rs7708392 with SLE, recently demonstrated in the Caucasian (European-American and Swedish) populations [12], was examined in a Japanese population. Departure from Hardy-Weinberg equilibrium was observed neither in the cases nor in the controls ($P > 0.3$). As shown in Table 2, rs7708392C allele was significantly increased in Japanese SLE patients (76.5%) compared with healthy controls (69.9%, $P = 0.0022$, OR 1.40, 95% confidence interval [95% CI] 1.13-1.74), confirming the association in the Caucasians. The association was also detected under the recessive model for the rs7708392C allele ($P = 0.0023$, OR 1.52, 95% CI 1.16-2.00). Notably, the risk allele frequency was considerably greater in the Japanese (69.9%) than in the Caucasian healthy controls (24.3%) [12]. In the Japanese, PAR% was estimated to be 20.4% under the recessive model for the C allele (OR 1.52, population frequency of C/C 49.8%) and 31.0% under the dominant model (OR 1.50, population frequency of C/C + C/G 90.8%). These estimates were substantially greater than in the Caucasian populations, where the PAR% was 3.0% under the recessive model (OR 1.53, population frequency of C/C 6.0%) and 14.1% under the dominant model (OR 1.39, population frequency of C/C + C/G 42.7%).

Because the female-to-male ratio was different between SLE patients and healthy controls (Table 1), we carried out multiple logistic regression analysis to examine the association after adjustment for gender. The association with SLE remained significant both under the recessive model for rs7708392C ($P = 0.030$, OR 1.40, 95% CI 1.03-1.89) and under the codominant model ($P = 0.033$, OR 1.30, 95% CI 1.02-1.65).

**Association of TNIP1 with Clinical Subsets of SLE**

We next analyzed whether TNIP1 was associated with clinical subsets such as presence or absence of renal disorder, neurological disease, serositis, anti-dsDNA antibody, anti-Sm antibody, as well as the age of onset (< 20 yr). When the association was tested between patients having each phenotype and healthy controls, a tendency of stronger association was observed in the subsets with renal disorder and anti-dsDNA antibody as compared with all SLE (Table 2). These associations remained significant after adjustment for gender using logistic regression analysis (nephropathy positive versus controls: $P = 0.0070$, OR 1.50, 95% CI 1.12-2.01 under the codominant model and $P = 0.011$, OR 1.59, 95% CI 1.11-2.26 under the recessive model; anti-dsDNA positive versus controls: $P = 0.033$, OR 1.32, 95% CI 1.02-1.71 under the codominant model and $P = 0.024$, OR 1.45, 95% CI 1.05-2.00 under the recessive model).

On the other hand, significant association was not observed in the patient subsets having neurologic disease, serositis, anti-Sm antibody, and the patients with the age of onset < 20 yr.

**Lack of Association with RA**

We next tested association of TNIP1 rs7708392 with RA. Although a slight tendency toward association was observed, significant association with RA was not detected (Table 3). Significant association was not detected after the adjustment for gender ($P = 0.847$, OR 1.02, 95% CI 0.83-1.26 under the codominant model, $P = 0.753$, OR 1.04, 95% CI 0.80-1.36 under the recessive model), nor after stratification according to the presence or absence of HLA-DRB1 shared epitope (Table 3).
Lack of Evidence for Genetic Interaction between TNFAIP3 and TNIP1

Finally, we examined whether genetic interaction exists between TNFAIP3 and TNIP1 SNPs, because molecular interaction is known between the protein products of these genes. Although all combinations of the codominant, dominant and recessive models for each gene were examined, statistically significant gene-gene interaction was not detected (P >0.05).

Discussion

In the present study, we replicated the association of TNIP1 rs7708392 with SLE in a Japanese population, which indicated that TNIP1, as well as TNFAIP3, is a susceptibility gene to SLE shared by the Caucasian and Asian populations. Because both TNIP1 and A20 are thought to be involved in the inhibition of NF-κB activation, genetic association of these genes implicates a causal role of NF-κB regulation pathway in the pathogenesis of SLE.

Kalergis et al. [24] demonstrated that expression of lnxB-α, an inhibitor of NF-κB, was decreased in Fcy receptor IIB-deficient mice which present lupus-like symptoms, and the symptoms were reduced by treatment with NF-κB inhibitors. Previous studies demonstrated that TNFAIP3 risk allele rs2230926G (127Cys) leads to reduced inhibitory activity of NF-κB activation [6] or reduced mRNA level of TNFAIP3 [10]. In view of these observations, it is speculated that the risk allele of TNIP1 may also be associated with reduced inhibitory activity of TNFAIP3-TNIP1 pathway.

TNIP1 rs7708392 is located in intron 1. Expression analysis using the GENEVAR [25] and the International HapMap databases [26] as previously described [27] did not show significant effect of rs7708392 genotypes on the mRNA level of TNIP1 (data not shown). Although the direct molecular mechanism of the risk allele to cause SLE remains unclear, it is possible that the risk allele may be associated with the selection of splicing

| Genotype | Allele | Allelic association | Recessive model* |
|----------|--------|---------------------|------------------|
| C/C      | C/G    | G/G                | C               | P     | OR (95%CI) | P     | OR (95%CI) |
| 216 (59.3) | 125 (34.3) | 23 (6.3) | 557 (76.5) | 0.0022 | 1.40 (1.13-1.74) | 0.0023 | 1.52 (1.16-2.00) |

Table 2 Association study of TNIP1 rs7708392 with SLE in a Japanese population

**Table 3 Association study of TNIP1 rs7708392 with RA in a Japanese population**

| Genotype | Allele | Allelic association | Recessive Model* |
|----------|--------|---------------------|------------------|
| C/C      | C/G    | G/G                | C               | P     | OR (95%CI) | P     | OR (95%CI) |

**Table 3 Association study of TNIP1 rs7708392 with RA in a Japanese population**

OR: odds ratio, 95% CI: confidence interval. Genotype and allele frequencies are shown in parentheses (%). Association was tested by χ² analysis using 2 × 2 contingency tables. Comparisons were made between all RA and all healthy controls, HLA-DRB1 shared epitope positive RA and controls, and shared epitope negative RA and controls.

*Association was tested under the recessive model for rs7708392C allele.
variant. To date, at least 11 splice variants of *TNIP1* have been identified [1]. Presence of alternative exon 1A and 1B, as well as splice variants lacking exon 2, has been described. Because rs7708392 is located between exon 1B and exon 2, it is possible that this SNP may influence the usage of the splicing isoform. It is also possible that other causative SNPs in tight LD with rs7708392 may exist. Such a possibility would be addressed by resequencing the entire *TNIP1* gene.

Interestingly, in sharp contrast to the Caucasian populations, the risk rs7708392C constituted the major allele in the Japanese population. This resulted in substantially higher PAR% in the latter. We previously reported similar findings in *STAT4* and *BLK* SNPs [14,15]. In Chinese, a SNP rs10036748, which is in tight LD with rs7708392 in Japanese ($r^2 = 0.81$, HapMap database [26]), has been shown to be associated with SLE. The frequencies of rs10036748 risk allele in Chinese (cases 79.7%, controls 66.1%) [8] are similar to those of rs7708392 in Japanese (Table 2). It should be noted that, because the information used to estimate the PAR % was based on the data from a variant that has not been shown to be the causal variant in *TNIP1*, and the estimates of the allele frequency and OR (as an approximation for RR) were taken from a rather small case-control study, the PAR% values shown here represent rough estimates. Nevertheless, the data suggest that the significance of *TNIP1* in the genetic background of SLE may be substantially greater in the Asian than in the Caucasian populations.

In the association analysis with the clinical subsets, none of the case-only comparisons (cases with each clinical phenotype versus those without) reached statistical significance, partly because of the insufficient statistical power caused by the small sample size due to stratification. However, preferential association of *TNIP1* with renal disorder and anti-dsDNA antibody was suggested by comparison with healthy controls. In our subjects, preferential association with renal disorder was also observed for *TNFAIP3* [10].

On the other hand, association was not observed with the SLE subsets having neurological disease, serositis, anti-Sm antibody and age of onset <20. It is interesting to note that renal disorder and presence of anti-dsDNA are significantly correlated in SLE, while neurologic disorders are not, suggesting that these clinical features might represent different clinical subsets of SLE [28]. In view of this, our findings could be interpreted such that polymorphisms in *TNIP1-TNFAIP3* pathway might play a significant role in the subset of SLE characterized by renal disorder and anti-dsDNA antibody, but not in the subset with neurologic disease. Such a hypothesis should be validated in future large-scale studies.

No strong evidence for association of rs7708392 with RA was obtained in this study. The sample size in this study (553 RA patients and 513 controls) provides 80% power to detect associations with genotype relative risk of 1.32 or greater, but we cannot rule out a possibility of weak association. Recently published meta-analysis of GWAS in Caucasians also failed to demonstrate statistically significant association of *TNIP1* SNP with RA, although similarly to our observation, a tendency for association was detected [29]. Thus, while a role of *TNFAIP3* is observed both in SLE and RA genetics, *TNIP1* appears to play a major role in SLE, but not in RA. Such a difference might possibly imply that the molecular mechanism of *TNIP1* association might not be fully explained by A20 modification. In support of this possibility, TNIP1 has been shown to block TNF-induced programmed cell death in *TNFAIP3* deficient cells, indicating that TNIP1 does not always require A20 to perform its anti-apoptotic function [3]. Thus, further analysis on the molecular mechanisms involving these molecules is required.

**Conclusions**

Association of *TNIP1* with SLE was confirmed in a Japanese population. *TNIP1* is a shared SLE susceptibility gene in the Caucasian and Asian populations, but the genetic contribution appeared to be greater in the Asians because of the higher risk allele frequency in the population. Taken together with the association of *TNFAIP3*, these observations underscore the crucial role of NF-κB regulation in the pathogenesis of SLE.

**Abbreviations**

95%CI: 95% confidence interval; ABIN-1: A20-binding inhibitor of NF-κB -1; CI: confidence interval; GWAS: genome-wide association studies; HLA-DRB1: human leukocyte antigen DR B1; LD: linkage disequilibrium; NF-κB: nuclear factor-κB; OR: odds ratio; PAR%: population attributable risk percentage; PCR: polymerase chain reaction; RA: rheumatoid arthritis; RR: relative risk; SLE: systemic lupus erythematosus; SNP: single nucleotide polymorphism; TNFAIP3: tumor necrosis factor α-induced protein 3; TNIP1: TNFAIP3 interacting protein 1.

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Authors’ contributions
AK participated in the study design, carried out all genotyping and statistical analyses, and wrote the manuscript. JO carried out statistical analysis with AK and helped in the manuscript preparation. SI, HF, TH, DG, IM, MK, KM, ST, YT, HH and TS recruited Japanese patients with SLE and collected clinical information. RRG and TWB provided Caucasian data. NT designed and coordinated the study and helped in the manuscript preparation. All authors read and approved the final manuscript.

Competing interests
RRG and TWB are employees of Genentech, Inc. (South San Francisco, CA, USA). The other authors declare that they have no competing interests.

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