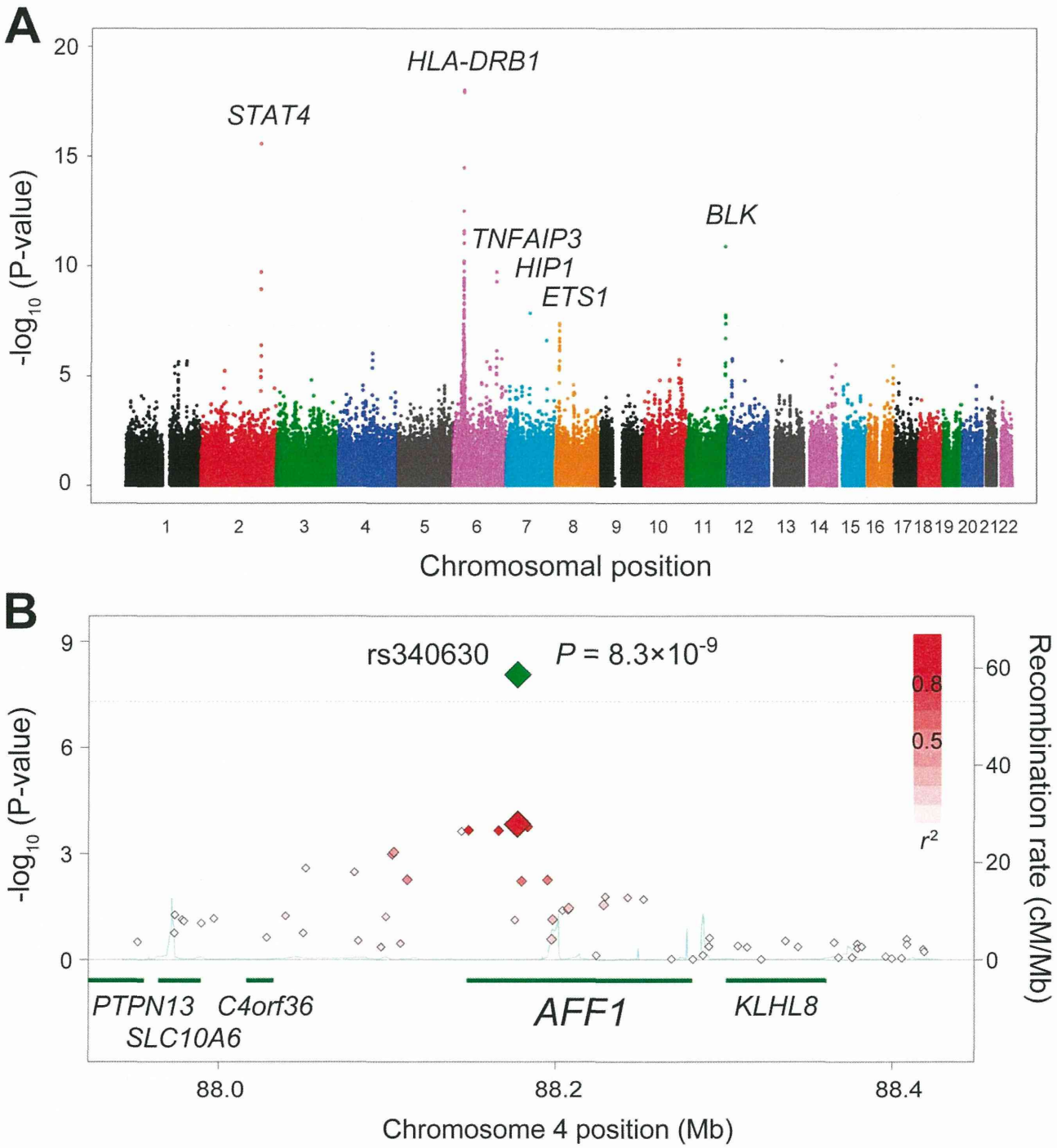

Figure 2. Associations of the *AFF1* locus with SLE. (A) A chromosomal plot of *P*-values in GWAS for SLE. (B) A regional plot in the *AFF1* locus. Diamond-shaped data points represent $-\log_{10}$ (*P*-values) of the SNPs. Large-sized points indicate the *P*-values of the landmark SNP, rs340630 (green for the combined study and red for the GWAS). Density of red color represents r^2 values with rs340630. Blue line represents recombination rates. Lower part indicates RefSeq genes. Gray dashed horizontal lines represent the threshold of $P = 5.0 \times 10^{-8}$. The plots were drawn using SNAP, version 2.1 [47].
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Medical University, the University of Tokyo, and the BioBank Japan Project [36]. All subjects were of Japanese origin and provided written informed consent. SLE cases met the revised American College of Rheumatology (ACR) criteria for SLE [37]. Control subjects were confirmed to be free of autoimmune disease. Some of the SLE cases were included in our previous studies [38–40]. Details of the subjects are summarized in Table S1 and S2. This research project was approved by the ethical committees of the University of Tokyo, RIKEN, and affiliated medical institutes.

Table 2. Associations among previously reported SLE-related loci.

rsID	Chr	Position (bp)	Cytoband	Gene	Allele[a]	Allele 1 freq.		OR (95%CI)	*P*	eQTL[b]	Identified by the studies in[c]	
					1/2	Case	Control				Caucasians	Asians
rs2205960	1	171,458,098	1q25	*TNFSF4*	T/G	0.23	0.18	1.35 (1.19–1.54)	3.0×10^{-6}		+	
rs3024505	1	205,006,527	1q32	*IL10*	A/G	0.019	0.014	1.34 (0.90–2.00)	0.15		+	
rs13385731	2	33,555,394	2p22	*RASGRP3*	C/T	0.90	0.87	1.37 (1.15–1.64)	6.0×10^{-4}	+		+
rs10168266	2	191,644,049	2q32	*STAT4*	T/C	0.37	0.27	1.59 (1.42–1.78)	2.7×10^{-16}		+	
rs6445975	3	58,345,217	3p14	*PXK*	G/T	0.25	0.23	1.09 (0.96–1.23)	0.18	+	+	
rs10516487	4	102,970,099	4q24	*BANK1*	G/A	0.91	0.89	1.28 (1.07–1.53)	0.0070		+	
rs10036748	5	150,438,339	5q33	*TNIP1*	T/C	0.75	0.72	1.16 (1.03–1.31)	0.014			+
rs9501626	6	32,508,322	6p21	*HLA-DRB1*	A/C	0.20	0.12	1.86 (1.62–2.13)	1.0×10^{-18}		+	
rs548234	6	106,674,727	6q21	*PRDM1*	C/T	0.40	0.34	1.30 (1.16–1.44)	2.3×10^{-6}	+	+	
rs2230926	6	138,237,759	6q23	*TNFAIP3*	G/T	0.11	0.069	1.75 (1.47–2.08)	1.9×10^{-10}	+	+	
rs849142	7	28,152,416	7p15	*JAZF1*	C/T	0.999	0.999	2.72 (0.25–29.8)	0.41		+	
rs4917014	7	50,276,409	7p12	*IKZF1*	T/G	0.58	0.53	1.24 (1.11–1.38)	8.1×10^{-5}			+
rs6964720	7	75,018,280	7q11	*HIP1*	G/A	0.25	0.19	1.43 (1.27–1.62)	1.3×10^{-8}			+
rs4728142	7	128,361,203	7q32	*IRF5*	A/G	0.16	0.11	1.48 (1.28–1.72)	2.4×10^{-7}	+	+	
rs2254546	8	11,381,089	8p23	*BLK*	G/A	0.78	0.72	1.42 (1.25–1.61)	4.1×10^{-8}	+	+	
rs1913517	10	49,789,060	10q11	*WDFY4*	A/G	0.32	0.28	1.20 (1.07–1.35)	0.0013			+
rs4963128	11	579,564	11p15	*KIAA1542*	T/C	0.98	0.97	1.58 (1.03–2.44)	0.038	+	+	
rs2732552	11	35,041,168	11p13	*PDHX, CD44*	T/C	0.75	0.73	1.13 (1.00–1.27)	0.056		+	
rs4639966	11	118,078,729	11q23	Intergenic	T/C	0.32	0.28	1.22 (1.09–1.36)	7.3×10^{-4}			+
rs6590330	11	127,816,269	11q24	*ETS1*	A/G	0.48	0.39	1.44 (1.30–1.60)	1.3×10^{-11}			+
rs1385374	12	127,866,647	12q24	*SLC15A4*	T/C	0.19	0.16	1.21 (1.06–1.38)	0.0057			+
rs7329174	13	40,456,110	13q14	*ELF1*	G/A	0.30	0.25	1.32 (1.18–1.49)	2.2×10^{-6}			+
rs7197475	16	30,550,368	16p11	Intergenic	T/C	0.12	0.10	1.20 (1.02–0.41)	0.031			+
rs11150610	16	31,241,737	16p11	*ITGAM*	C/A	0.20	0.19	1.07 (0.94–1.22)	0.32	+	+	
rs12949531	17	13,674,531	17p12	Intergenic	T/C	0.28	0.27	1.02 (0.91–1.15)	0.73		+	
rs463426	22	20,139,185	22q11	*HIC2,UBE2L3*	T/C	0.52	0.48	1.20 (1.08–1.33)	6.1×10^{-4}		+	

[a]Based on forward strand of NCBI Build 36.3.
[b]Defined using gene expression data measured in lymphoblastoid B cell lines [28].
[c]Based on the previously reported studies for SLE susceptibility loci [3–18].
SLE, systemic lupus erythematosus; OR, odds ratio; eQTL, expression quantitative trait locus; GWAS, genome-wide association study.
doi:10.1371/journal.pgen.1002455.t002

Genotyping and quality control

In GWAS, 946 SLE cases and 3,477 controls were genotyped using Illumina HumanHap610-Quad and Illumina HumanHap550v3 Genotyping BeadChips (Illumina, CA, USA), respectively. After the exclusion of 47 SLE cases and 92 controls with call rates <0.98, SNPs with call rates <0.99 in SLE cases or controls,

Table 3. Results of combined study for Japanese patients with SLE.

rsID	Chr	Position (bp)	Cytoband	Gene	Allele	Stage	No. subjects		Allele 1 freq.		OR (95%CI)	*P*	eQTL[a]
					1/2		Case	Control	Case	Control			
rs340630	4	88,177,419	4q21	*AFF1*	A/G	GWAS	891	3,383	0.56	0.51	1.22 (1.10–1.36)	1.5×10^{-4}	+
						Replication study 1	550	646	0.57	0.49	1.40 (1.19–1.64)	4.6×10^{-5}	
						Replication study 2	820	27,911	0.56	0.53	1.14 (1.03–1.26)	0.0094	
						Combined study	2,261	31,940	0.56	0.52	1.21 (1.14–1.30)	8.3×10^{-9}	

[a]Defined using gene expression data measured in lymphoblastoid B cell lines [28].
doi:10.1371/journal.pgen.1002455.t003

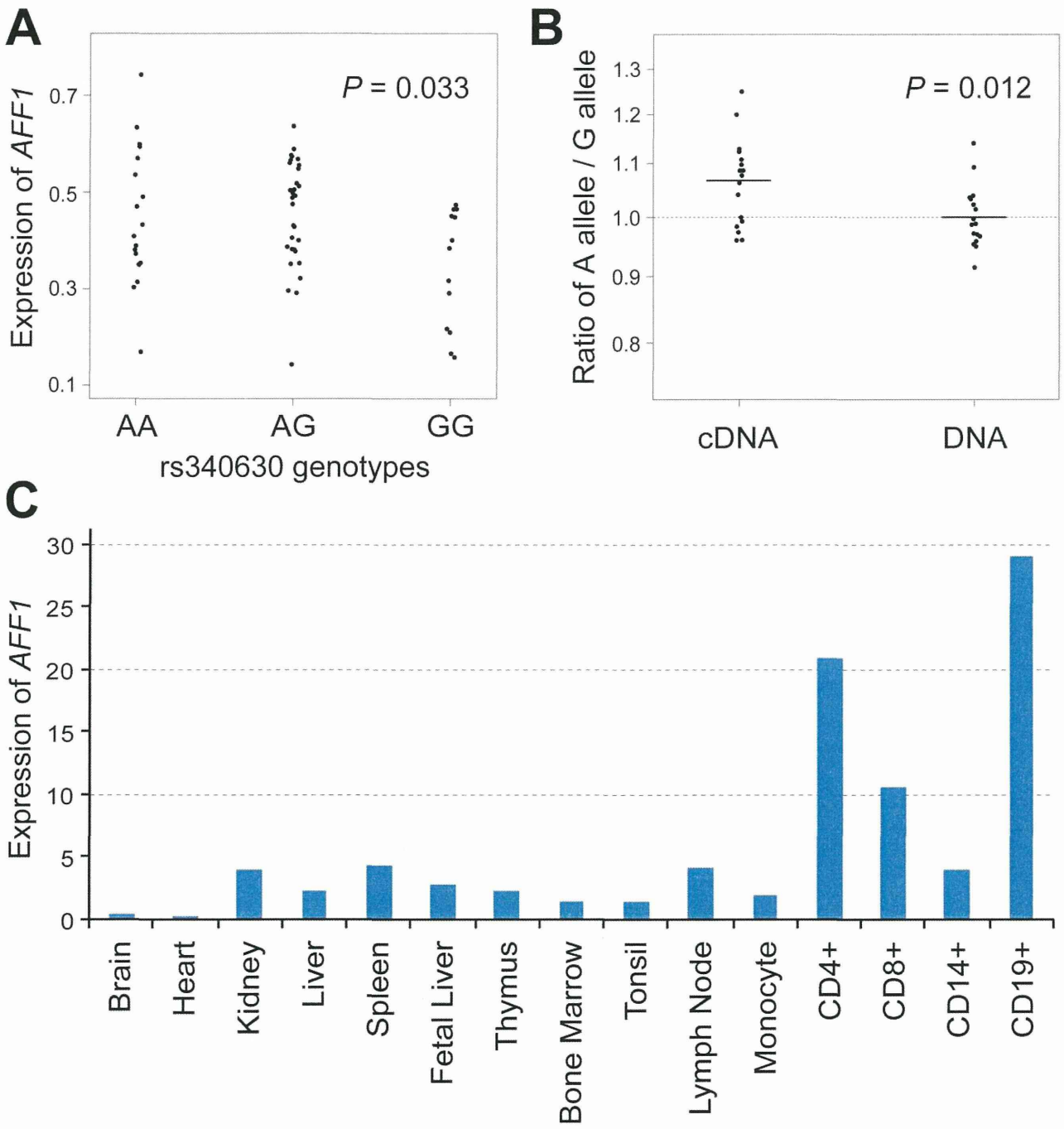

Figure 3. Association of rs340630 with *AFF1* expression. (A) Correlation between rs340630 genotypes and transcript levels of *AFF1* (NM_001166693) in EBV-transfected cell lines ($n = 62$) stimulated with PMA. (B) Allele-specific quantification (ASTQ) of *AFF1* transcripts. Allele specific-probes for rs340638 were used for quantification by qPCR. The ratios of A allele over G allele for the amounts of both cDNAs and DNAs were plotted in log scale for each cell line. (C) *AFF1* expression in various tissues. Transcripts levels of *AFF1* were quantified by qPCR and were normalized by *GAPDH* levels.
doi:10.1371/journal.pgen.1002455.g003

non-autosomal SNPs, and SNPs not shared between SLE cases and controls, were excluded. We excluded 7 closely related SLE cases in a 1st or 2nd degree of kinship based on identity-by-descent estimated using PLINK version 1.06 [41]. We then excluded 1 SLE cases and 1 controls whose ancestries were estimated to be distinct from East-Asian populations using PCA performed along with the genotype data of Phase II HapMap populations (release 24) [29] using EIGENSTRAT version 2.0 [42]. Subsequently, SNPs with minor allele frequencies <0.01 in SLE cases or controls, SNPs with exact *P*-values of Hardy-Weinberg equilibrium test $<1.0\times10^{-6}$ in controls, or SNPs with ambiguous cluster plots were excluded. Finally, 430,797 SNPs for 891 SLE cases and 3,384 controls were obtained. Genotyping of SNPs in replication studies was performed using TaqMan Assay or Illumina HumanHap610-Quad Genotyping BeadChip (Illumina, CA, USA).

Association analysis of the SNPs

Association of SNPs in GWAS and replication studies were tested with Cochran-Armitage's trend test. Combined analysis was performed with Mantel-Haenzel method. Associations of previously reported SLE susceptibility loci [3–18] were evaluated using the results of the GWAS. Genotype imputation was performed for non-genotyped SNPs using MACH version 1.0 [43] with Phase II HapMap East-Asian individuals as references [29], as previously described [44]. All imputed SNPs demonstrated imputation scores, *Rsq*, >0.70.

eQTL study

We analyzed gene expression data previously measured in lymphoblastoid B cell lines from Phase II HapMap East-Asian individuals using Illumina's human whole-genome expression array (WG-6 version 1) (accession number; GSE6536) [28]. Expression data were normalized across the individuals. We used BLAST to map 47,294 Illumina array probes onto human autosomal reference genome sequences (Build 36). We discarded probes mapped with expectation values smaller than 0.01 to multiple loci, or for which there was polymorphic HapMap SNP(s) inside the probe. Then, 19,047 probes with exact matches to a unique locus with 100% identity and with a mean signal intensity greater than background were obtained. Genotype data of HapMap individuals were obtained for SNPs included in the GWAS. Associations of SNP genotypes (coded as 0, 1, and 2) with expression levels of each of the cis-eQTL probes (located within ±300 kbp regions of the SNPs) were evaluated using linear regression assuming additive effects of the genotypes on the expression levels. Considering the significant overlap between eQTL and genetic loci responsible for autoimmune diseases [24], we applied relatively less stringent multiple testing threshold of FDR *Q*-values<0.2 for the definition of eQTL. SNPs that exhibited this threshold with any of the corresponding cis-eQTL probes were denoted as eQTL positive.

Selection of SNPs enrolled in the replication studies

In order to select SNPs for further replication studies, we firstly integrated the results of GWAS and eQTL study. SNPs that satisfied $P<1.0\times10^{-4}$ in GWAS, or the SNPs that satisfied $1.0\times10^{-4}\leq P<1.0\times10^{-3}$ in GWAS and denoted as eQTL positive, were selected. Among these, SNPs most significantly associated in each of the genomic loci and not included in the previously reported SLE susceptibility loci [3–18] were further evaluated.

Then, the results of the concurrently proceeding genome-wide scan for SLE in the Japanese subjects using a pooled DNA approach were referred (Tahira T et al. Presented at the 59th Annual Meeting of the American Society of Human Genetics, October 21, 2009). In the scan, DNA collected from 447 SLE cases and 680 controls of Japanese origin were pooled respectively, and genotyped using GeneChip Human Mapping 500K Array Set (Affymetrix, CA, USA). SNPs were ranked according to the Silhouette scores estimated based on relative allele scores (RAS) between SLE cases and controls, and rank-based *P*-values were assigned [30]. By referring to association signals in multiple neighboring SNPs in the pooled analysis, we selected SNPs for replication study 1. Namely, if the SNP of interest was in LD ($r^2>0.5$) or was located within ±100 kbp of SNPs showing association signals in the pooled analysis (rank-based $P<0.01$), it would be selected. SNPs that satisfied $P<1.0\times10^{-6}$ in the combined study of GWAS and replication study 1 were further evaluated in replication study 2 (Figure 1).

Quantification of *AFF1* expression

EBV-transformed lymphoblastoid cell lines ($n=62$) were established by Pharma SNP Consortium (Tokyo, Japan) using peripheral blood lymphocytes of Japanese healthy individuals. Cells were incubated for 2 h in medium alone (RPMI 1640 medium containing 10% FBS, 1% penicillin, and 1% streptomycin) or with 100 ng/ml PMA. Conditions for cell stimulation were optimized before the experiment as previously described [45]. Cells were then harvested and total RNA was isolated using an RNeasy Mini Kit (Qiagen) with DNase treatment. Total RNA (1 μg) was reverse transcribed using TaqMan Gold RT-PCR reagents with random hexamers (Applied Biosystems). Real-time quantitative PCR was performed in triplicate using an ABI PRISM 7900 and TaqMan gene expression assays (Applied Biosystems). Specific probes (Hs01089428_m1) for transcript of *AFF1* (NM_001166693) were used. Expression of *AFF1* in various tissues was also quantified using Premium Total RNA (Clontech). The data were normalized to *GAPDH* levels. *GUS* levels were also evaluated for internal control, and similar results were obtained. Correlation coefficient, R^2, between rs340630 genotypes and transcript levels of *AFF1* was evaluated.

Allele-specific transcript quantification (ASTQ)

ASTQ of *AFF1* in PSC cells was performed as previously described [46]. DNAs were extracted by using a DNeasy Kit (QIAGEN). RNA extraction and cDNA preparation were performed as described above. For PSC cells ($n=17$) that were heterozygous for both rs340630 (the landmark SNP of GWAS) and rs340638 (located in the 5′-untranslated region of *AFF1* and in absolute LD with rs340630), expression levels of *AFF1* were quantified by qPCR on an ABI Prism 7900 using a custom-made TaqMan MGB-probe set for rs340638. Primer sequences were 5′-CTAACTGTGGCCCGCGTTG-3′ and 5′-CCCGGCGCAGTTTCTGAG-3′. The probe sequences were 5′-VIC-CGAAGACCGCCAGCGCCCAAC-TAMRA-3′ and 5′-FAM-CGAAGACCGCCGGCGCCCAA-TAMRA-3′. Ct values of VIC and FAM were obtained for genomic DNA and cDNA samples after 40 cycles of real-time PCR. We also prepared genomic DNA of samples homozygous for each allele and mixed them at different ratios (2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2) to create a standard curve by plotting Ct values of VIC/FAM against the allelic ratio of VIC/FAM for each mixture. Using the standard curve, we calculated the allelic ratios for each genomic DNA and cDNA samples. We measured each sample in quadruplicate in one assay; tests were independently repeated twice.

Web resources

The URLs for data presented herein are as follows.

NCBI GEO, http://www.ncbi.nlm.nih.gov/geo

BioBank Japan Project, http://biobankjp.org

PLINK software, http://pngu.mgh.harvard.edu/~purcell/plink/index.shtml

International HapMap Project, http://www.hapmap.org

EIGENSTRAT software, http://genepath.med.harvard.edu/~reich/Software.htm

MACH and mach2qtl software, http://www.sph.umich.edu/csg/abecasis/MACH/index.html

SNAP, http://www.broadinstitute.org/mpg/snap/index.php

Supporting Information

Figure S1 Principal component analysis (PCA) plot of the subjects. PCA plot of subjects enrolled in the GWAS for SLE. SLE cases and the controls enrolled in the GWAS are plotted based on

eigenvectors 1 and 2 obtained from the PCA using EIGENSTRAT version 2.0 [42], along with European (CEU), African (YRI), Japanese (JPT), and Chinese (CHB) individuals obtained from the Phase II HapMap database (release 22) [29]. Subjects who were estimated to be outliers in terms of ancestry from East-Asian (JPT+CHB) clusters and excluded from the study are indicated by black arrows.
(TIF)

Figure S2 Quantile-Quantile plot (QQ-plot) of *P*-values in the GWAS for SLE. The horizontal axis indicates the expected $-\log_{10}$ (*P*-values). The vertical axis indicates the observed $-\log_{10}$ (*P*-values). The QQ-plot for the *P*-values of all SNPs that passed the quality control criteria is indicated in blue. The QQ-plot for the *P*-values after the removal of SNPs included in the previously reported SLE susceptibility loci is indicated in black. The gray line represents $y = x$. The SNPs for which the *P*-value was smaller than 1.0×10^{-15} are indicated at the upper limit of the plot.
(TIF)

Table S1 Basal characteristics of cohorts.
(DOC)

Table S2 Frequency of clinical characteristics of SLE in this GWAS.
(DOC)

Table S3 Distributions of eQTL positivity rates of the SNPs.
(DOC)

Table S4 Results of replication study 1 for Japanese patients with SLE.
(DOC)

Table S5 Results of replication studies 1 and 2 for Japanese patients with SLE.
(DOC)

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Author Contributions

Conceived and designed the experiments: Y. Okada, K. Shimane, Y. Kochi, A. Suzuki, M. Kubo, N. Kamatani, R. Yamada, Y. Nakamura, K. Yamamoto. Performed the experiments: Y. Kochi, N. Hosono, M. Kubo, K. Myouzen, T. Horiuchi, T. Tahira, K. Hayashi. Analyzed the data: Y. Okada, A. Takahashi, T. Tsunoda, K. Higasa, R. Yamada. Contributed reagents/materials/analysis tools: T. Horita, T. Atsumi, T. Koike, T. Ishii, A. Okamoto, K. Fujio, M. Hirakata, H. Amano, Y. Takasaki, Y. Kondo, S. Ito, T. Sumida, K. Takada, A. Mimori, K. Saito, Y. Tanaka, M. Kamachi, N. Nishimoto, Y. Kawaguchi, C. Terao, K. Ohmura, T. Mimori, F. Matsuda, O.W. Mohammed, K. Matsuda, K. Shimane, K. Ikari, H. Yamanaka. Wrote the paper: Y. Okada, K. Shimane, Y. Kochi, A. Suzuki, R. Yamada, K. Yamamoto.

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CASE REPORT

Etanercept is safely used for treating psoriatic arthritis in a patient complicated with type 1 hereditary angioedema

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Abstract Hereditary angioedema (HAE) is a life-threatening disorder caused by deficiency or dysfunction of the C1 inhibitor protein. Patients with HAE are restricted in various medical treatments, which can induce an HAE attack. We herein report the first case of psoriatic arthritis (PSA) with type 1 HAE successfully treated with 25 mg of etanercept without HAE attack. Etanercept may represent a useful choice for treating patients with HAE accompanied by intractable PSA and rheumatoid arthritis (RA).

Keywords Psoriatic arthritis · Hereditary angioedema · Biological agent · Etanercept

Introduction

Hereditary angioedema (HAE) is a rare autosomal dominant disorder caused by deficiency or dysfunction of the C1 inhibitor (C1-INH) protein. Patients with HAE have intermittent acute attacks of edema involving the larynx, oropharynx, face, gastrointestinal mucosa, extremities, or genitalia [1]. Edema of the larynx can result in asphyxiation, with mortality rates as high as 30% if the condition is left undiagnosed and untreated [2]. It is known that HAE attacks can be induced by trauma, such as dental procedures, and biological agents might also cause an HAE attack by activating complement and reducing C1-INH. We herein report the first case of psoriatic arthritis (PSA) with HAE safely and successfully treated by etanercept.

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Case

A 42-year-old Japanese woman experienced several episodes of local edematous swelling of her skin since age 30. Her mother had experienced more frequent episodes, with facial and laryngeal edema lasting 6 months, and was diagnosed with HAE based on the reduced activity of C1-INH noted by the previous clinic. The patient was also diagnosed with psoriasis that appeared as scaly erythematous plaques on almost her entire body beginning at 15 years of age. At the age of 40, she developed a fever, morning stiffness, and severe arthritis on her bilateral fingers and toes. Despite the use of combination therapy with cyclosporine, salazosulfapyridine, and bucillamine administered orally, her arthritis remained active. After surgery for an infectious cyst in the maxilla, administration of methotrexate (MTX) (4 mg/week) was started and thereafter was increased to 6 mg/week; however, it was not effective.

The patient's laboratory findings were as follows: white blood cells 4,650/μl, red blood cells 3.56×10^6/μl, platelets 12.3×10^4/μl, hemoglobin 11.1 g/dl, hematocrit 33.5%, C-reactive protein (CRP) 0.23 mg/dl, matrix

metalloproteinase-3 (MMP-3) 69.1 ng/ml, C3 107 mg/dl, C4 <2 mg/dl (17–45 mg/dl), CH50 <10.0 U/ml (25–46 U/ml), activity of C1-INH <25% (80–152%), serum interleukin-6 (IL-6) 44.5 pg/ml (<4 pg/ml), and serum tumor necrosis factor alpha (TNF)-α 2.9 pg/ml. There were positive test results for antinuclear antibodies (ANA) (1:320 speckled pattern), anti-SSA antibodies, anti-RNP antibodies, and rheumatoid factor; results were negative for anti-CCP antibodies, anti-double-stranded DNA (anti-dsDNA) antibodies, and anti-Sm antibodies. Human leukocyte antigen (HLA) typing indicated A2, B46, and DR8. technetium-99m bone scintigraphy revealed a high accumulation in the sternoclavicular joint, proximal and distal interphalangeal joints of the bilateral fingers and toes, and sacroiliac joint. Serial radiographic examinations demonstrated rapidly progressive destruction of the interphalangeal joints. The patient's disease activity scale (DAS)28 erythrocyte sedimentation rate (ESR) was 3.05 (moderate). Her Psoriasis Area and Severity Index (PASI) was 15. A genetic analysis of the C1 inhibitor demonstrated a T-to-G transition at nucleotide position 1269 in exon 8 (c.1269 T>G), which caused a nonsense mutation at amino acid residue 401(p.Y401 stop) [7] The patient's plasma C1-INH protein level was significantly decreased (1.4 mg/dl) compared with normal control (15–35 mg/dl). The same mutation was detected in her mother and in her daughter. Taken together, a diagnosis of PSA with type 1 HAE was made.

Because of the patient's poor response to conventional therapy, the administration of 25 mg of etanercept twice weekly with 1,500 mg of tranexamic acid was started. In 8 weeks, the patient's painful swollen joints, fever, and anemia all improved. Her DAS28-ESR decreased to 2.35, and her PASI reached a level of almost 0, and these results were evaluated as a good response. No HAE attack or major adverse effects were observed.

Discussion

To the best of our knowledge, this is the first report of a biological agent being administered to a patient with probable type 1 HAE. Type 1 HAE, which is caused by a deficiency in the amount of C1-INH protein, is present in up to 85% of all HAE patients. C1-INH is the main regulator of the early activation steps of the classical complement pathway. C1-INH also regulates the activation of kallikrein, plasmin in the fibrinolytic pathway, and activation of factor XII in the coagulation cascade. C1-INH deficiency results in increased vascular permeability and local edema. The HAE attack may be induced by trauma, medical/dental procedures (e.g., surgery), infections, menstruation, contraceptive use, and the use of certain mediations, such as angiotensin-converting enzyme (ACE) inhibitors [2, 3]. Biological agents might also induce an HAE attack by activating the complement cascade and the subsequent reduction of the C1-INH. However, little is known about the effects of biological agents in HAE patients [4]. We made a decision to use etanercept to treat our PSA patient because we considered that etanercept had a lower risk of inducing HAE attacks compared with other biological agents due to its structural advantage.

Etanercept, which is effective for PSA and rheumatoid arthritis (RA), exerts its action by binding to TNF in serum, thus inhibiting its ability to interact with its cell-surface receptors that promote the inflammatory process. Etanercept is a fusion protein composed of the p75 TNF-receptor linked to the Fc protein of human Immunoglobulin (Ig)G1, the CH2 domain of which activates C1. However, etanercept dose not carry the CH1 domain of IgG1, which is essential for activating C3, the most important step in complement activation cascade [5]. In fact, etanercept has been shown to have almost negligible complement-activating ability [6]. It is therefore considered that etanercept might be less likely to induce HAE attacks compared with other antibody-type biologics administered for psoriasis, such as infliximab and adalimumab.

In many cases, patients with HAE are restricted in terms of the type of medical treatment they can receive for their complications because of the risk of a treatment-induced attack. Despite the limited amount of data, etanercept may represent a useful choice for treating patients with HAE accompanied by intractable PSA and RA. Careful observation and further studies are needed to confirm the safety indications for biological agents for patients with HAE.

Conflict of interest None.

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TNF 受容体関連周期性症候群

(TNF receptor-associated periodic syndrome: TRAPS)

診療ガイドライン 2012（案）

厚生労働科学研究費補助金　難治性疾患克服研究事業

「TNF受容体関連周期性症候群（TRAPS）の病態の解明と
診断基準作成に関する研究」研究班

「TNF受容体関連周期性症候群（TRAPS）の病態の解明と診断基準作成に関する研究」研究班（平成22年～24年度）

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【疾患の概要】

TNF受容体関連周期性症候群（TNF receptor-associated periodic syndrome: TRAPS）は、常染色体優性の家族性周期性発熱疾患である。繰り返す発熱に加えて、皮疹、筋痛、関節痛、腹痛、胸痛、結膜炎、眼窩周囲浮腫など多彩な症状を呈する代表的な自己炎症疾患の一つである[1-4]。

2010年度に本研究班が行なった全国調査によって、本邦では過去の報告とも合わせ少なくとも30数家系いることが判明した。また症例の蓄積によって本邦TRAPS患者の特徴も明らかになってきた。こうした現状をふまえて本ガイドラインは作成された。

【臨床像】

TRAPSの臨床症状は多彩であるが、ほぼ100%必発するのは繰り返す発熱である。発作期には、38℃以上の発熱とともに、関節痛、皮疹（写真１）、腹痛、筋痛、結膜炎・眼窩周囲浮腫（写真２）、胸痛などの随伴症状を伴う。発症年齢は乳児期より成人まで幅広いが多くは20歳未満で発症する。これらの症状は5日以上持続することが多い。通常は1か月未満で終息するが、発作が数か月続いた報告がある。発作の頻度は月1回から年1回程度であることが多い。周期性症候群と命名されているが、実際には発作の間隔は不定期である。

表1に本邦TRAPS25家系の37名について症状別の頻度を示すとともに、欧米患者の症状も提示する。

本邦におけるTRAPSには、大きく二つの特徴がある。一つは発熱に加えて、関節痛、皮疹は欧米と同程度で約50%の患者に認めるが、腹痛、筋痛、結膜炎・眼窩周囲浮腫、胸痛などの症状は有意に少ない。

もう一つの特徴は、本邦TRAPS患者で認められるTNFRSF1A遺伝子（*TNFRSF1A*）の異常は二つの種類があることである。すなわち健常人にはその異常を認めない「変異」と、健常人にもきわめて低頻度であるが認める「バリアント（variant）」の二つである。バリアントとして本邦ではT61Iが報告されており、TRAPS症状を呈する患者に比較的多く認められる。

変異は14家系に24名の報告がある[5-11]。種類はさまざまで、C15Y, N25D, C30Y, C30R, T50M, C70S, C70G, C88Y, N101K, V125M, V136M, S321Iがある。C30Y, T50Mのみ2家系報告されているが、それ以外は1家系ずつ報告されている。家族歴を71%に認める。

一方、バリアントであるT61Iについては10家系、13名について解析した[12,13]。臨床症状については変異例と大きな違いはないが、家族歴をほとんど認めないことより遺伝的リスクとは考えにくい。従って狭義のTRAPS（変異例）には含めないこととした。

検査所見で特徴的なものはない。発作時には、ほとんどの症例で、白血球、CRP、赤沈、補体など非特異的な炎症マーカーが高値となる。

表 1　本邦 TRAPS 患者と欧米 TRAPS 患者の症状の比較

主要症状・所見	**本邦全体 (n=37)**	変異 (n=24)	variant (n=13)	**欧米[14] (n=153)**
発熱（38℃以上）	**97%**	100%	92%	**記載なし**
関節痛	**59%**	58%	62%	**51%**
皮疹	**49%**	38%	69%	**55%**
腹痛*	**35%**	33%	38%	**77%**
筋痛*	**30%**	29%	31%	**64%**
結膜炎・眼窩周囲浮腫*	**19%**	8%	38%	**49%**
胸痛*	**3%**	0%	8%	**32%**
5日以上続く	**84%**	79%	92%	**記載なし**
20歳未満の発症	**76%**	75%	77%	**記載なし**
家族歴あり*	**46%**	71%	20%	**82%**

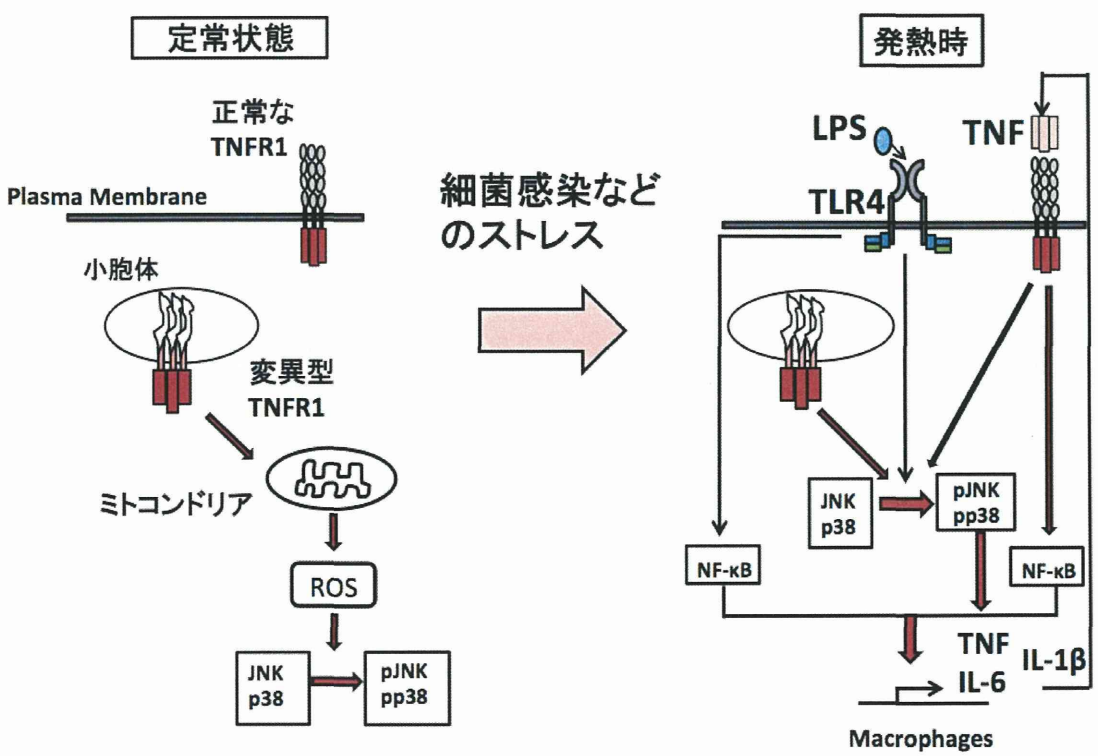
*　：$p<0.01$　（本邦全体 vs 欧米）

【病態】

TRAPSの原因となる遺伝子異常は、TNF受容体1型の遺伝子（*TNFRSF1A*）の異常である。さまざまな人種から100を超える変異が報告されている[15]。変異のほとんどは単一塩基ミスセンス変異による単一アミノ酸の変異である。変異はTNF受容体1型の細胞外ドメインの4つのCRD(cysteine-rich domain)のうちのN末側の3つに集中している。特にタンパクの形状を保つS-S結合を形成するシステイン残基の変異が多い。

これらの変異がTRAPSの病態にいかに関与するかについては不明な点が多かったが、近年その機序が解明されつつある[16-18]。TNF受容体1型の遺伝子変異によりタンパクのmisfolding（折りたたみ不良）が生じ、小胞体内の品質管理機構により変異タンパクは小胞体内に停滞する。このストレスによって、細胞内のミトコンドリアが刺激され活性酸素種（reactive oxygen species, ROS）が産生される。その結果細胞内のMAPK脱リン酸化酵素を阻害することにより定常状態でMAPKを活性化状態にする。これだけでは炎症性サイトカインの誘導は起こらないが、細菌感染などでToll様受容体からの活性化シグナルが加わることにより、IL-1β, IL-6, TNFなどのサイトカイン産生誘導が起こると考えられる。このようにして産生されたTNFは片方の対立遺伝子由来の正常に細胞表面に表出したTNF受容体に作用してパラクライン的に炎症を増幅させる。

以上のメカニズムでTRAPSの病態をある程度説明できるようになったが、TRAPSの病態をすべて説明することはできない。さらなる病態の解明が必要である。



文献 16-18)より引用、改変

【診断方法】

TNF受容体1型遺伝子（*TNFRSF1A*）異常を認めることが、診断の根拠として重要である。

診断は、疑い症例の拾い出し、診断の確定、の2段階で行う。

第一段階：疑い症例の拾い出し

1）HullらのTRAPS診断基準（案）*

2）全身性若年性特発性関節炎（systemic JIA）あるいは成人スチル病(AOSD)と診断されているが典型的ではない**

1）、2）のいずれかを満たす症例は第二段階の検討を行う。

*Hullらの診断基準（案）[2)]

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1. 6か月以上反復する炎症症候の存在（いくつかは同時に見られることが一般的）
   （1）発熱
   （2）腹痛
   （3）筋痛（移動性）
   （4）皮疹（筋痛に伴う紅斑様皮疹）
   （5）結膜炎・眼窩周囲浮腫
   （6）胸痛
   （7）関節痛、あるいは単関節滑膜炎
2. 症状が平均5日以上持続（有症状期間はさまざま）
3. ステロイドが有効かつコルヒチンが無効
4. 家族歴あり（ただし孤発例もありうる）
5. どの人種、民族でも起こりうる

**複数のTRAPS症例は、確定診断される前に「典型的ではないsystemic JIAもしくはAOSD」と診断されている。「典型的ではない」とは、皮疹がリウマトイド疹（サーモンピンク、ケブネル現象を伴う）ではない、関節症状がない、フェリチン上昇がない、何回も発作を繰り返すことをさす。

第二段階：診断の確定

1．発作（5日以上）を繰り返す

2．20歳未満の発症

3．家族歴

この3項目（TRAPS 遺伝子解析スコア）のいずれか2項目を有する場合にはTNF受

容体1型遺伝子（*TNFRSF1A*）の異常を有している可能性が高いため、*TNFRSF1A*の遺伝子解析を行う。遺伝子異常があればTRAPSと確定診断する。

「TRAPS 遺伝子解析スコア」を利用した場合に、本邦TRAPS患者でTNF受容体1型遺伝子異常が同定される感度は90.0%、特異度は69.8%であった。

追記）

1）TRAPS 様の症状を呈する患者で、TNF 受容体 1 型遺伝子（*TNFRSF1A*）異常を認めない場合には、「TRAPS 疑い」とする。将来、TNF 受容体あるいは関連分子に異常が見つかる可能性がある。

2）当研究班では 2 施設で TRAPS 判定のための遺伝子解析を行っている。

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【治療法】

発作期間が短く、頻度も少ない症例は、発作時のNSAIDや副腎皮質ステロイドの頓用のみで対応されているが、発作期間が長い症例、頻回に起こる症例では、やむを得ず副腎皮質ステロイドやエタネルセプトの長期投与が行われている。

本邦ではアミロイドーシスを合併したとの報告はほとんどないが、欧米ではとくにシステイン変異例に稀ならず報告されており[2]、注意が必要である。

1）副腎皮質ステロイド

・発作の重症度や発作期間の短縮に有効な場合が多い。

・通常プレドニゾロン換算で最大30mg／日より開始し、7～10日間で減量、中止する。

・当初効果があった症例でも次第に効果が減弱し、増量や継続投与を強いられる場合もある。その際にはエタネルセプト併用を考慮する。

2）エタネルセプトetanercept（商品名エンブレル）

・TNF受容体2型の細胞外ドメインとIgGのFc部分との融合タンパクであり、TNF阻害作用を示す。エタネルセプト投与により発作の重症度の軽減や発作頻度の減少を認めるが、無効例や注射部位の疼痛で投与中止を余儀なくされる例もまれではない[19]。

・成人：エタネルセプト25mgを週2回皮下注、小児：0.4mg/kgを週2回皮下注

・発作が消失すれば原則中止するが、継続投与を必要とする症例もある

3）アナキンラanakinra

・IL-1受容体の拮抗薬である。有効であったとする報告が散見される[20]。

・国内では販売されていない。

4）トシリズマブtocilizumab（商品名アクテムラ）

・IL-6受容体に対する抗体であり、IL-6の作用を阻害する。エタネルセプトとアナキンラに無効であった症例に投与して有効であったことが報告されている[21]。

5）その他の治療法

・家族性地中海熱と異なりコルヒチンの有効性は低い。

・非ステロイド性抗炎症薬（NSAID）のみでコントロールできる症例も一部には存在する。

・抗TNF抗体であるインフリキシマブinfliximab（商品名レミケード）は、むしろ症状を悪化させる場合がある[22]。

・抗IL-1β抗体であるカナキヌマブcanakinumabは有効性が期待されている。

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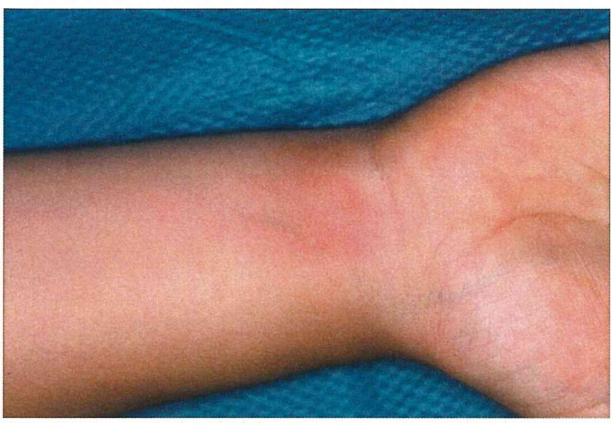
写真１　TRAPS の皮疹は、斑状の紅斑であることが多い。
斑状の紅斑であることが多い。写真はともに前腕の皮疹であるが、躯幹に出現することもある。ケブネル現象を伴わない。
（産業医科大学小児科　楠原浩一教授　提供）



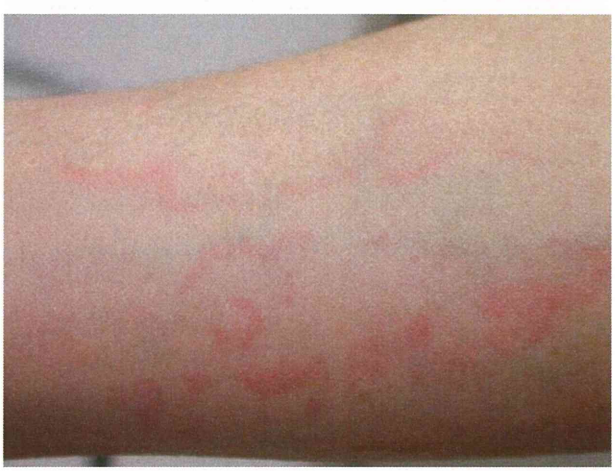


写真２　結膜炎を発作時に認めることがある。
（九州大学大学院病態修復内科学　堀内孝彦准教授　提供）